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Toward the Two-Directional Synthesis of the IJK-Ring System of the Marine Polyether CTX3C

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Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

University of Glasgow

School of Chemistry
College of Science and Engineering

University of Glasgow

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Abstract

This thesis describes efforts made towards the two-directional synthesis of the IJK-tricyclic core of the H-M ring system of CTX3C.

The first chapter serves as an introduction to the complex marine polyether natural products and details their toxicology and biosynthetic origins. A literature review of the advances made by our research group, as well as in other laboratories, towards the iterative and convergent synthesis of polycyclic ethers, with particular emphasis on the ciguatoxins is also included. This is followed by a review of olefin metathesis and the use of double ring-closing metathesis reactions for the preparation of complex polycyclic systems.

The second chapter details the construction of two model systems to allow for investigation into the chemistry required for the synthesis of both the I- and K-rings. Following the successful construction of the two model systems, the chemistry developed was then employed in a two-directional strategy toward the synthesis of the target IJK-tricyclic core.
Declaration

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I further declare that the work presented in this manuscript is the result of my own investigation. Where the work of others has been utilised, this has been acknowledged in the appropriate manner.

Helen Gibbard

Prof. J. Stephen Clark
Acknowledgements

First and foremost, I would like to thank Professor J. Stephen Clark for giving me the opportunity to work on such a challenging and rewarding project. I appreciate all the advice and support he has given me over the past three years. I would also like to extend my gratitude to Dr Alistair Boyer for all his help and advice.

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Thanks to Geoff for all his patience, support and encouragement during the past couple of years.

Finally, I would like to thank my parents. I am fortunate to have such an understanding and supportive family.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’-azobis(2-methylpropionitrile)</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>i-Bu</td>
<td>iso-butyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>ºC</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
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<td>CSA</td>
<td>10-camphorsulfonic acid</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPA</td>
<td>diisopropylamine</td>
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<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>dimethyl dioxirane</td>
</tr>
<tr>
<td>DME</td>
<td>dimethyl ether</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
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<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone</td>
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<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>dppf</td>
<td>diphenylphosphinoferrocene</td>
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<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<tr>
<td>DTBMP</td>
<td>2,6-di-tert-butyl-4-methylpyridine</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximum effective concentration</td>
</tr>
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<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
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<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>EE</td>
<td>ethoxyether</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
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<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>L</td>
<td>litre</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>median lethal dose</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>molar</td>
</tr>
<tr>
<td>m-CPBA</td>
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</tr>
<tr>
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</tr>
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<td>mesityl</td>
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</tr>
<tr>
<td>MOM</td>
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<tr>
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<td>MS</td>
<td>molecular sieves</td>
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<td>NAP</td>
<td>2-napthylmethyl</td>
</tr>
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<td>NCS</td>
<td>N-chloro succinimide</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methylmorpholine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<td>pyridinium dichromate</td>
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<td>PG</td>
<td>protecting group</td>
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<td>pivaloyl</td>
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<tr>
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<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-propyl</td>
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<tr>
<td>Py</td>
<td>pyridine</td>
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</tbody>
</table>
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Chapter 1: Introduction
Chapter 1: Introduction

1.0 Marine Natural Products

Marine organisms have proven to be rich reservoirs of structurally diverse natural products.\(^1\) Many of these compounds display complex molecular architectures and potent toxicities. Several marine natural products have been identified as the causative agents in various seafood-related poisonings. These include compounds that cause diarrhetic shellfish poisoning (okadaic acid, 1),\(^2\) amnesic shellfish poisoning (domoic acid, 2),\(^3\) paralytic shellfish poisoning (saxitoxin, 3)\(^4\) and ciguatera (CTX3C, 4) (Figure 1).\(^5\)
1.1 Ciguatera and the Ciguatoxins

Ciguatera is a form of food poisoning that results from the consumption of tropical and sub-tropical coral reef fish that have been contaminated with marine biotoxins. It is a debilitating disease that results in numerous disorders affecting the gastrointestinal, neurological and cardiovascular systems. These symptoms can persist for weeks, months or even years. It has been estimated, that worldwide around 10000–50000 individuals suffer from this form of poisoning every year. With the rapid development of tourism and the growing international trade in seafood, poisoning of this type has become a potential threat on a global scale. It has been estimated that only 2–10% of cases are documented by health authorities as a consequence of misdiagnosis and under-reporting.

In 1977, Yasumoto and co-workers discovered that ciguatoxins, the principle causative agents of ciguatera, were produced by the epiphytic dinoflagellate Gambierdiscus toxicus. These biotoxins can be transferred to the herbivorous and carnivorous fish through the aquatic food chain. Over 400 species of coral reef fish have been identified as vectors of the ciguatera toxins, which accumulate in all fish tissues.

In 1989, the structure of ciguatoxin CTX1B (5) was successfully elucidated by Yasumoto and co-workers using 0.35 mg of the toxin extracted from moray eels (Gymnthurax javanicus) (Figure 2). Shortly after, the structures of CTX3C (4) and 51-hydroxyCTX3C (7) were reported. Studies have determined that ciguatoxins isolated from fish of the Pacific Ocean (4–7) show structural distinctions from those isolated from fish of the Caribbean Sea (8). To date, over 20 different structural congeners of ciguatoxin have been isolated and characterised.
1.2 Marine Polycyclic Ethers

The ciguatoxins belong to the marine polyether class of natural products. Other members of the polycyclic ether family include hemibrevitoxin B (9), brevetoxins A (10) and B (11), and gambierol (12) (Figure 3).
These polyether compounds are characterised by a single carbon chain locked into a long, semi-rigid, ladder-like structure. They contain distinctive extended arrays of trans-fused cyclic ethers that range in size from five- to nine-membered. The oxygen atoms of the ether rings are placed alternatively on the northern and southern edges of the molecule. The stereochemistry of the carbon atoms adjacent to the oxygen strictly alternates between $R$ and $S$ configuration (Figure 4).
1.3 Toxicology and Therapy

Ciguatoxins and brevetoxins are known to affect the function of various cell types (nerve, heart and muscle cells) by binding to the voltage-sensitive sodium channels of excitable membranes. These transmembrane ion channels are heteromeric proteins consisting of α- and β-subunits that are activated upon changes in electrical membrane potential. Upon binding to the α-subunit of the ion channel protein, these toxins induce a conformational change resulting in the persistent activation of the channel. The resultant prolonged depolarization causes a continuous influx of sodium ions and neurotransmitter release, which ultimately leads to blockage of impulse conduction and a failure in transmitter release. Binding of the toxins to the ion channel protein is believed to occur primarily through hydrogen bonding and/or electrostatic forces. Figure 5 highlights the possible interactions between the α-helix peptide and the ladder-like polyether. The average distance between the oxygen atoms on one side of the polyether structure matches the pitch of the α-helix.

Figure 5
Pharmacological studies have revealed that the toxicity of these molecules is associated with two main structural factors: the molecular size of the polyether and its conformational flexibility.\(^1^9\) The first of these factors accounts for the low toxicity of tetracyclic hemibrevetoxin B (9). Conformational flexibility explains the lower toxicity of brevetoxin B (11) when compared to brevetoxin A (10) and CTX3C (4). Brevetoxin B (11) has a more rigid conformation imposed by the longer \textit{trans}-fused sequence of six-membered rings. Both 10 and 4 have more flexible conformations due to the presence of seven-, eight- and nine-membered rings in the central region of the molecules.

Through the biological evaluation of F-ring analogues of 51-hydroxyCTX3C (7), Hirama and co-workers demonstrated the structural importance of the nine-membered F-ring.\(^2^1\) Synthetic analogues 13 and 14 were subjected to various biological assays: ligand-receptor interaction, \textit{in vitro} activity and \textit{in vivo} activity (\textit{Table 1}). Both the \textit{in vitro} and \textit{in vivo} activities for analogues 13 and 14 were notably weaker than those observed for 7, a finding that is consistent with the diminished affinities for the target receptor. Clearly, alterations in the F-ring structure have a significant effect on the bioactivity of the corresponding analogues.

![Chemical structures of molecules](image)

<table>
<thead>
<tr>
<th>Polyether</th>
<th>Receptor interaction(^{[a]})</th>
<th>Cytotoxicity(^{[b]})</th>
<th>Acute toxicity(^{[c]})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(K_i) [nm]</td>
<td>(EC_{50}) [nm]</td>
<td>(LD_{50}) [(\mu)g kg(^{-1})]</td>
</tr>
<tr>
<td>7</td>
<td>0.0646</td>
<td>0.00326</td>
<td>0.31</td>
</tr>
<tr>
<td>13</td>
<td>11.2</td>
<td>103</td>
<td>&gt; 667</td>
</tr>
<tr>
<td>14</td>
<td>125</td>
<td>170</td>
<td>&gt; 667</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Dissociation constants measured against 5.0 nm \[^{[3]}\text{H}\]·11.

\(^{[b]}\) Cytotoxicity determined as the \(EC_{50}\) value of mouse neuroblastoma cells Neuro-2A.

\(^{[c]}\) Acute toxicity determined as the \(LD_{50}\) value in intraperitoneal injected mice.

\textit{Table 1} \(^{2^1}\)
A victim of ciguatera poisoning usually experiences the onset of symptoms within six to twenty four hours of eating the contaminated fish. Gastrointestinal problems common to other types of food poisoning such as nausea, vomiting and diarrhoea are followed by neurological symptoms that include dizziness, numbness, headaches and a sensation of temperature reversal. Despite recent advances in the understanding of the pharmacological properties of ciguatoxins, no direct treatment for ciguatera poisoning has been identified. Treatment options focus primarily on the relief of symptoms: these include opiates for pain, along with antiemetic agents.

Recently, attention has turned toward the development of new antibody-based therapeutic methods for the treatment of ciguatera poisoning. Hirama and co-workers have shown that CTX3C (4) can be effectively neutralized in vitro and in vivo through the simultaneous use of two anti-ciguatoxin monoclonal antibodies. The monoclonal antibodies, specific against both ends of CTX3C (4), were prepared by immunization of mice with protein conjugates of two synthetic haptens 15 and 16 (Figure 6). This work is the first step in a process leading toward the in vivo detoxification of ciguatoxins by the rational application of monoclonal antibodies. The next step is to produce effective and safe ciguatoxin antibodies suitable for human treatment.
1.4 Biosynthesis of the Marine Polycyclic Ethers

To date, research into the biosynthetic origin of fused polycyclic ethers has focussed on the brevetoxins. The polycyclic ether skeleton was initially thought to be constructed through the standard polyketide pathway, in which linear Claisen-type condensations of acetate units form the carbon backbone. Through $^{13}$C-labelled studies, Nakanishi and Shimizu investigated the origin of the carbon atoms in the carbon backbone of both brevetoxins A (10) and B (11). In the standard polyketide pathway, the acetate-derived carbons are expected to be arranged in head-to-tail linkage. However, the $^{13}$C-labelled studies of the brevetoxins revealed that some of the carboxyl-derived carbons were missing from the carbon skeleton. This data suggested that the brevetoxins were mixed polyketides whose biosynthesis required the use of dicarboxylic acids (Scheme 1).

\[
\begin{align*}
\text{Scheme 1}^{26} \\
\end{align*}
\]

For several years, it has been postulated that nature synthesises the complex polycyclic ethers and other related natural products utilizing tandem oxacyclizations to construct several rings and multiple stereocentres in an efficient manner. Nakanishi and co-workers proposed that a cascade reaction involving polyepoxide precursor 17 may be responsible for the enzymatic controlled biosynthesis of brevetoxin B (11) (Scheme 2).\textsuperscript{1, 16a} Successive ring closure of polyepoxide 17 can be initiated upon attack of the carboxylate anion at the left terminus of the carbon chain (pathway A, Scheme 2). Shimizu and co-workers proposed an alternative pathway, involving intramolecular attack of a hydroxyl group on the right terminus of the carbon chain which triggers the cascade reaction of polyepoxide 18 in the opposite direction (pathway B, Scheme 2).\textsuperscript{15a, 27} The cascade reaction of either polyepoxide precursor requires disfavoured endo-tet $S_N2$ reactions, which violate Baldwin’s rules for ring closure.\textsuperscript{30}
For those hoping to employ a cascade strategy in the synthesis of selected polyether subunits, work by Coxon and co-workers has shown that cyclization of simple epoxy alcohols 19 typically proceed through a spiro transition state to afford the corresponding exo-product 21 (Scheme 3).
Recently, Jamison and co-workers have reported the development of *endo*-selective epoxide-opening cascades in water.\textsuperscript{32} They have been able to utilise a THP template in order to alter the approach of the alcohol nucleophile to the epoxide electrophile and so bias the substrate towards *endo* cyclization (Scheme 4).\textsuperscript{33} It is believed that the water molecules facilitate *endo* cyclization by forming a hydrogen-bonding network that bridges the oxygen atom within the THP template and the oxygen atom of the hydroxyl group attached to the template. These interactions encourage reorganization of the epoxy alcohol from an energetically favourable chair conformation into a higher energy twist boat conformation.\textsuperscript{33} Reaction through conformer 23 significantly alters the trajectory of nucleophilic attack by the epoxy alcohol. Theoretical studies have indicated that the most important factor dictating regioselectivity in epoxy alcohol cyclizations is the angle with which the alcohol approaches the epoxide, with an incidence angle of 100° being optimal.\textsuperscript{34} Such a trajectory is ideal because it allows for maximum overlap between the hydroxyl lone pair and the C—O\(_{\text{epox}}\) \(\sigma^*\) orbital.\textsuperscript{32}

![Scheme 4](image-url)
2.0 Strategies for the Synthesis of Ciguatoxins

The large and complex molecular architecture displayed by the marine polycyclic ethers dictates the need for highly efficient synthetic strategies. Numerous synthetic chemists have studied the development of new strategies and efficient methodologies for the construction of polycyclic ether ring systems. Nicolaou and co-workers have proven to be pioneers in the field of marine polyether synthesis. They reported the first total synthesis of a marine polyether, that of hemibrevetoxin B (9), in 1992 and have since completed the total syntheses of several larger members of this class of natural product. The following section looks at the strategies employed by various research groups for the synthesis of CTX3C (4) and other ciguatoxins.

2.1 Sasaki Group Approach

2.1.1 Suzuki Coupling/Reductive Etherification

In 1998, Sasaki and co-workers reported a strategy for the convergent synthesis of trans-fused polyether arrays that used palladium(0)-catalysed cross-coupling of alkylboranes with enol triflates (Scheme 5). Hydroboration of the exocyclic enol ether 26 using 9-BBN provided the corresponding alkylborane 27. Reaction between 27 and enol triflate 28 under Suzuki-Miyaura coupling conditions furnished the desired cross-coupled product 29. Stereoselective hydroboration of enol ether 29 with thexylborane followed by oxidative work-up and subsequent oxidation of the resultant secondary alcohol afforded ketone 30. Acidic removal of the silyl and acetonide groups followed by acetylation provided hemiketal 31. Finally, reductive etherification of 31 furnished the trans-fused pentacyclic ether 32.
Sasaki and co-workers utilized this methodology for the synthesis of the A-E ring system 39 of CTX3C (4) (Scheme 6). Treatment of the AB-ring olefin 33 with 9-BBN afforded the corresponding alkylborane, which was then reacted in situ under Suzuki-Miyaura coupling conditions with phosphate 34 to afford the cross-coupled product 35. Due to the chemical lability of medium-sized enol triflates, phosphate 34 was used as a stable alternative. From enol ether 35, four synthetic steps furnished the seven-membered D-ring. The required double bond was introduced to the D-ring via Saegusa oxidation to afford enone 36. Cleavage of the 4-methoxybenzyl ether and subsequent treatment with methyl orthoformate under acidic conditions provided mixed ketal 37. Acetal reduction then furnished the target pentacyclic array 38. Elaboration of the intermediate to the target A-E ring system 39 required introduction of both the A- and E-ring olefins.
Scheme 6

Sasaki and co-workers have also reported a highly convergent synthetic route to the right-hand F-M ring system 40 of CTX1B (5). Once again, their strategy relied upon the extensive use of the Suzuki-Miyaura coupling reaction (Figure 7).
Utilizing their developed methodology, FG-ring olefin 41 and enol phosphate 42 were successfully coupled to afford enol ether 43 (Scheme 7). A short synthetic sequence furnished the tetracyclic ring system 44. A second Suzuki coupling reaction between the exo-enol ether 44 and triflate 45 delivered the cross-coupled product 46. Elaboration from enol ether 46 delivered the target F-M ring system 40 of CTX1B (5).

a) 9-BBN, THF; then 42, Pd(PPh₃)₄, NaHCO₃ aq., DMF, 85%; b) 9-BBN, THF; then 45, Pd(PPh₃)₄, Cs₂CO₃ aq., DMF, 61%.

Scheme 7
2.1.2 O,O-Acetalization/Intramolecular Radical Cyclization

Sasaki and co-workers have also reported a strategy for the synthesis of the O-linked oxepane ring system 53 based on an intramolecular radical cyclization reaction (Scheme 8).40

- **47** + **48** → **49**
  - a) CSA, benzene, 80 °C, quant.;
  - b) i-Bu2AlSePh, PhMe, -20 °C, 94%;
  - c) 1. MOMCl, i-Pr2NEt, CH2Cl2;
  - 2. TBAF, THF; 3. methyl propiolate, Bu3P, CH2Cl2, 69% (3 steps);
  - d) n-Bu3SnH, Et3B, benzene, 66%.

**Scheme 8**
Acetalization between diol 47 and aldehyde 48 afforded the six-membered acetal 49 (Scheme 8). Regioselective cleavage of the less hindered C–O acetal bond in 49 yielded the monoselenoacetal 50 as a single stereoisomer.\textsuperscript{41} Protection of the hydroxyl group as the corresponding methoxymethyl ether followed by removal of the silyl ether and treatment with methyl propiolate in the presence of tributylphosphine furnished the desired β-alkoxyacrylate 51.\textsuperscript{42} It was found that β-alkoxyacrylate 51 favoured the extended s-trans- over the s-cis-conformation in order to avoid 1,3-diaxial-like interactions. Radical cyclization, upon treatment with tributyltin hydride in the presence of triethylborane, provided the O-linked oxacycle 53.\textsuperscript{43} The stereochemical outcome of the reaction was rationalized upon consideration of the transition state conformers 52a and 52b. In 52b steric congestion between the acrylate unit and the bulky alkoxy group attached to the radical centre is avoided.

Sasaki and co-workers reported an efficient route to the FGH-ring system 60 of CTX1B (5) utilizing the developed intramolecular radical cyclization methodology combined with a RCM reaction (Scheme 9).\textsuperscript{44} Treatment of diol 47 with β-benzylxyaldehyde 54 in the presence of scandium triflate afforded the desired six-membered acetal 55 as a single stereoisomer in good yield. Acetal 55 was then elaborated to the GH-ring system 56 upon conversion to the mixed selenoacetal and subsequent radical cyclization. Reduction of 56 followed by Wittig methylenation of the resultant aldehyde furnished olefin 57. Removal of the methoxymethyl ether followed by activation of the primary alcohol by conversion to the triflate and subsequent displacement with lithium (trimethylsilyl)acetylide provided silylacetylene 58. Removal of the trimethylsilyl group followed by partial hydrogenation using Lindlar catalyst furnished diene 59. Finally, treatment of diene 59 with Grubbs first generation catalyst 61 led to the formation of the nine-membered F-ring and completion of the FGH-ring system 60 of CTX1B (5).\textsuperscript{45}
a) Sc(OTf)$_3$, benzene, 80%; b) 1. DIBAL, CH$_2$Cl$_2$, −78 ºC; 2. Ph$_3$PCH$_2$Br, NaHMDS, 0 ºC, 77% (2 steps); c) 1. BF$_3$·Et$_2$O, Me$_2$S, CH$_2$Cl$_2$, 0 ºC, 83%; 2. Tf$_2$O, 2,6-lutidine, CH$_2$Cl$_2$, −78 ºC; 3. Me$_3$SiCCH, n-BuLi, THF/HMPA, −78 ºC, 61% (2 steps); d) 1. K$_2$CO$_3$, THF/MeOH, 90%; 2. H$_2$, Lindlar catalyst, EtOAc, 86%; e) 61, CH$_2$Cl$_2$, 35 ºC, 61%.

Scheme 9
2.2 Hirama Group Approach

2.2.1 Intramolecular alkylation/RCM reaction

In 1998, Hirama and co-workers reported a new strategy for the synthesis of 6/7/7/6-tetracyclic polyether systems 62 ($n = 7–10$) (Figure 8).\(^{46}\)

![Figure 8](image)

Coupling of tert-butyl ester 63 with iodide 64 using lithium diisopropylamide afforded the desired compound 65 as the major isomer (Scheme 10). Removal of the silyl ether and subsequent treatment with $p$-toluenesulfonic acid furnished the six-membered lactone 66. Addition of vinylmagnesium bromide to 66 gave the corresponding hemiacetal which was then selectively reduced to give the O-linked oxacycle 67.\(^{47}\) Oxacycle 67 was then converted to diene 68 in three steps. Treatment of diene 68 with Grubbs first generation catalyst 61 delivered the target polyether system 69.\(^{46}\)

**Scheme 10**

- a) LDA, HMPA, THF, 61%;
- b) TBAF, THF; then cat. TsOH, PhMe, 90 °C, 84%;
- c) 1. CH$_2$CHMgBr, THF, −78 °C, 80%; 2. Et$_3$SiH, BF$_3$·Et$_2$O, MeCN, 71%;
- d) 61 (10 mol%), benzene, 81%.
Hirama and co-workers demonstrated the versatility of their developed alkylation-metathesis strategy through the synthesis of the A-E ring system 77 of CTX3C (4) (Scheme 11).48

Scheme 11

Unlike the model system detailed in Scheme 10,46 intermolecular alkylation between tert-butyl ester 71 and iodide 70 afforded an inseparable mixture of epimers 72 in favour of the undesired stereoisomer (C11R:C11S = 6:1). The undesired stereochemistry was addressed following the cyclization of diene 73 to alcohol 74. Oxidation of alcohol 74 followed by DBU-mediated epimerization furnished the more thermodynamically stable pseudoequatorial isomer 75-S as the major isomer. Removal of the 4-methoxybenzyl group, followed by
acetalization under acidic conditions afforded the pentacyclic polyether skeleton 76. Reductive etherification and subsequent functional group manipulations provided the target A-E ring system 77 of CTX3C (4).

In order to avoid the base-mediated epimerisation step, Hirama and co-workers developed an alternative approach to the A-E ring system 81 of CTX3C (4) (Scheme 12). The stereoselectivity of the alkylation step was successfully controlled through the incorporation of a chiral aminooindanol derivative into the substrate. The coupling reaction between iodide 78 and amide 79 afforded the desired isomer 80 exclusively. The stereoselectivity of the coupling reaction resulted from the attack of iodide 78 from the less hindered C11-si face of the kinetically and thermodynamically favoured Z-enolate of 79. Amide 80 was successfully elaborated to afford the required A-E ring system 81 of CTX3C (4).

\[ \text{78} \xrightarrow{\text{a}} \text{79} \rightarrow \text{80} \xrightarrow{\text{Scheme 12}} \text{81} \]

a) \( n \)-BuLi, DMPU, THF, 96%.

Scheme 12
2.2.2 Esterification/Intramolecular Enol Formation with RCM or Related Reaction

In 1996, Nicolaou and co-workers reported a new strategy for the synthesis of fused polyethers based on olefin metathesis,\(^{51}\) which facilitated the generation of cyclic enol ethers directly from an olefinic ester using either the Tebbe (Cp\(_2\)TiCH\(_2\)ClAlMe\(_2\)) or Petasis (Cp\(_2\)TiMe\(_2\)) reagent (Scheme 13).\(^{52}\) Olefinic ester A was converted to enol ether B upon treatment with the Tebbe reagent. It was proposed that the initially formed alkene then reacted with a second molecule of the Tebbe reagent to afford the titanacyclobutane C. Fragmentation of C afforded the titanium alkylidene D and intramolecular reaction of D then provided titancyclobutane E. Regioselective fragmentation furnished the desired cyclic enol ether F via olefin metathesis.

![Scheme 13](image)

Nicolaou and co-workers employed their olefin metathesis based strategy for the construction of several key fragments (82–84) of the large marine polyether natural product maitotoxin (Figure 9).\(^{53}\)
Hirama and co-workers attempted to utilize the developed metathesis strategy for the construction of the I-M ring system 93 of CTX3C (4) (Scheme 14). Unfortunately, the reaction to provide the desired cyclic enol ether 86 proved unreliable. Significant amounts of uncyclized ethers 87 and 88 were isolated and treatment of these compounds with the Tebbe reagent did not afford the desired cyclic enol ether 86. Steric hinderance around the diene system of 87/88 was blamed for the lack of cyclization observed.

As an alternative to the use of the Tebbe reagent, Hirama and co-workers employed the direct carbonyl olefination reaction of bis(phenylthio)acetals developed by Takeda (Scheme 15). Treatment of dithioacetal 91 with the low-valent titanium complex Cp₂Ti[P(OEt)₃]₂ generated the required enol ether 92 in a reproducible manner. Introduction of the seven-membered K-ring afforded the I-M ring system 93 of CTX3C (4).

Scheme 14
2.2.3 \textit{O,O}-Acetalization/Intramolecular Radical Cyclization

In 2001, Hirama and co-workers were the first to report the total synthesis of a ciguatoxin, that of CTX3C (4). Their synthesis employed a refined and modified version of Sasaki’s intramolecular radical cyclization strategy (see Ch 1, § 2.1.2). Their highly convergent strategy was based upon the coupling of the A-E ring system 94 and the H-M ring system 95 (Figure 10).
Scandium trifluoromethanesulfonate-promoted condensation between 1,4-diol 94 and β-alkoxy aldehyde 95 afforded the seven-membered acetal 96 (Scheme 16). Treatment of acetal 96 with phenylthiotrimethylsilane and trimethylsilyl trifluoromethanesulfonate furnished the linear O,S-acetal 97 without affecting the potentially reactive spiroketal. Construction of the seven-membered G-ring was realised upon stereoselective radical cyclization between the O,S-acetal and β-alkoxyacrylate. Treatment of 97 with tributyltin hydride and AIBN furnished the desired G-ring oxepane 98. Steric interactions between the bulky alkoxy group and β-alkoxyacrylate favoured the formation of desired isomer 98 (see Ch 1. § 2.1.2). Five steps were required for the conversion of 98 to the RCM precursor 99. The critical chemoselective RCM reaction of 99 to form the F-ring, without affecting any of the pre-existing di-substitututed double bonds, preceded smoothly using Grubbs first generation catalyst 61. Construction of the nine-membered F-ring provided the required polyether skeleton 100. Global deprotection of 100 with DDQ completed the first total synthesis of CTX3C (4).
a) Sc(OTf)$_3$, benzene, 91%; b) 1. TMSSPh, TMSOTf, DTBMP, then K$_2$CO$_3$, MeOH, 74%; 2. ethyl vinyl ether, PPTS, 99%; 3. TBAF, THF; 4. methyl propiolate, NMM, 89% (2 steps); c) n-Bu$_3$SnH, AIBN, PhMe, 85 ºC; d) 61 (20 mol%), CH$_2$Cl$_2$, 40 ºC, 90%; e) DDQ, CH$_2$Cl$_2$/H$_2$O, 63%.

Scheme 16
2.2.4 Direct O,S-Acetal Formation/Intramolecular Radical Cyclization

The protecting group strategies that could be employed in the first generation synthesis of CTX3C (4) were restricted by the use of a Lewis acid in both the acetalization step to form the O,O-acetal 96 and the subsequent conversion to the O,S-acetal 97 (Scheme 16).\(^{40, 56}\) This could potentially cause problems during the synthesis of other ciguatoxin congeners and so Hirama and co-workers developed a new, mild method for the construction of O,S-acetals that did not require strongly acidic conditions (Scheme 17).\(^{60}\) O,S-Acetal 103 was obtained upon the coupling of secondary alcohol 101 and α-chlorosulfide 102 using AgOTf.\(^{61}\) Halophilic activators, such as the silver cation, are highly chemoselective and non-acidic. This coupling strategy allows for the use of a wide variety of protecting groups.\(^{60}\)

\[
\begin{align*}
\text{101} & \quad + \quad \text{102} \\
& \quad \xrightarrow{a} \quad \text{103}
\end{align*}
\]

a) AgOTf, DTBMP, 4Å MS, CH\(_2\)Cl\(_2\), −60 ºC to −30 ºC.

Scheme 17

In 2004, Hirama and co-workers reported the second generation total synthesis of CTX3C (4).\(^{59, 62}\) Coupling of alcohol 104 and α-chlorosulfide 105 facilitated the direct construction of O,S-acetal 106 (Scheme 18). As well as the ability to employ a wider range of protecting groups, this strategy also required fewer steps because it was no longer necessary to proceed via the O,O-acetal. Following the direct construction of O,S-acetal 106, radical cyclization of 107 constructed the G-ring of 108 stereoselectively in 54% yield. By-product 109 arose from 6-exo cyclization of the radical onto the terminal olefin (27% yield).\(^{59}\) The synthesis was then completed in the same manner as the first generation strategy. The nine-membered F-ring was constructed via RCM reaction and subsequent elaboration to CTX3C (4) proceeded smoothly.
a) AgOTf, DTBMP, CCl₄/CH₂Cl₂, −50 ºC to −30 ºC, 70%; b) 1. TBAF, THF, 35 ºC, 85%; 2. methyl propiolate, NMM, CH₂Cl₂, quant.; c) n-Bu₃SnH, AIBN, PhMe, 85 ºC, 108: 54%, 109: 27%.

Scheme 18
Following their successful synthesis of CTX3C (4), Hirama and co-workers focussed their attention on the synthesis of other ciguatoxin congeners. Efforts to synthesise 51-hydroxyCTX3C (7) began with the coupling of the alcohol 104 and α-chlorosulfide 110 to afford O,S-acetal 111 (Scheme 19). A modified radical cyclization precursor was employed in order to avoid the unwanted 6-exo cyclization by-product observed during the second generation synthesis of CTX3C (4). Model studies revealed that the incorporation of the pentafluorophenyl group significantly improved the selectivity for the desired 7-exo cyclization. The required cyclization precursor 112 was synthesised in two steps from acetal 111 with the silyl ether exchanged for the pentafluorophenyl acrylate. Stereoselective radical cyclization provided the desired seven-membered G-ring 113. A short synthetic sequence allowed for elaboration of the acid 113 to the target 51-hydroxyCTX3C (7).
a) AgOTf, DTBMP, CH₂Cl₂:CCl₄ (5:1), −70 °C, 70%; b) 1. TBAF, THF, 35 °C, quant.; 2. pentafluorophenyl propiolate, PMe₃, CH₂Cl₂, 95%; c) n-Bu₃SnH, AIBN, PhMe, 85 °C, 74%.

Scheme 19
Having established a suitable synthetic route to 51-hydroxyCTX3C (7), attention turned toward the total synthesis of CTX1B (5) (Scheme 20). As well as displaying an additional dihydroxybutenyl side chain, CTX1B (5) possesses a seven-membered E-ring rather than the eight-membered E-ring present in both CTX3C (4) and 51-hydroxyCTX3C (7). The presence of the acid/base/oxidant-sensitive bisallylic C5-ether heightened the synthetic challenge posed by CTX1B (5). Despite these challenges, CTX1B (5) was successfully synthesised upon the coupling of the A-E ring system 114 and the H-M ring system 105.
2.3 Isobe Group Approach

2.3.1 Acetylide-Aldehyde Coupling/Cyclization of Acetylene Cobalt Complex

In 1994, Isobe and co-workers reported a novel approach to the synthesis of medium-sized cyclic ethers via cobalt-acetylene complexes (Scheme 21). The use of cobalt-acetylene complexes is well established in synthetic chemistry as a result of the introduction of the Pauson-Khand and Nicholas reactions. Coupling between the lithium acetylide generated from 116 and aldehyde 117 under Yamaguchi’s protocol afforded diol 118. The acetylinic moiety of 118 was converted into the corresponding acetylene-dicobalthexacarbonyl complex 119, which cyclized rapidly to give the endo-cobalt complex 120. Decomplexation with tri-n-butyltin hydride afforded bicyclic ether 121.

Utilizing their cobalt-acetylene strategy, Isobe and co-workers reported the synthesis of several regions of CTX1B (5), 122–124 (Figure 11). Following the successful synthesis of the B-E ring system 124 and H-M ring system 123, Isobe and co-workers focused on the coupling of these two fragments to complete the total synthesis of CTX1B (5).
Coupling between the lithium acetylide of 124 and aldehyde 123 furnished enyne 125 (Scheme 22). The hydroxyl groups of 125 were protected as acetates, and subsequent removal of the ethoxyethyl group provided the propargylic acetate 126. The acetylenic moiety of 126 was then converted into the corresponding acetylene-dicobalthexacarbonyl complex. Cyclization upon treatment with $p$-toluenesulfonic acid afforded the desired nine-membered F-ring 127 as a single stereoisomer. Oxidative decomplexation of complex 127 afforded ketone 128 and subsequent introduction of the seven-membered G-ring afforded the B-M ring system 129 of CTX1B (5).
Scheme 22

a) 1. n-BuLi, THF, −78 °C; 2. TBAF, THF, 54% (2 steps); b) 1. Ac₂O, pyridine, DMAP; 2. Amberlyst 15, MeOH, 77% (2 steps); c) 1. Co₂(CO)₈, CH₂Cl₂; 2. TsOH·H₂O, CH₂Cl₂, 72% (2 steps); d) (Ph₂P)₂CH₂, PhMe, N₂, 100 °C, then air, 100 °C, 48%.
Sonogashira coupling between the B-M ring system 131 and the \textit{trans}-vinylidioide 130 furnished enyne 132 (Scheme 23).\textsuperscript{70} The seven-membered A-ring was then introduced \textit{via} the developed acetylene-dicobalthexacarbonyl strategy. Reductive decomplexation of the \textit{endo}-complex 133 followed by global deprotection afforded CTX1B (5).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{a) 1. DDQ, diallyl ether, ClCH}_2\text{CH}_2\text{Cl, 55 °C, 68%; 2. Pd(PPh}_3\text{)}_4, CuI, n-PrNH}_2, PhMe, 60%;
\node (b) at (0,-1) {\textbf{b) 1. Co}_2(CO)_8, CH}_2\text{Cl}_2, 70%; 2. TMSOTf, CH}_2\text{Cl}_2, -20 °C, then THF, 70%.
\end{tikzpicture}
\end{center}
2.4 Clark Group Approach

2.4.1 Two-Directional Double RCM

Clark and co-workers have reported several robust strategies for the synthesis of polycyclic ether systems utilizing RCM methodology. The target cyclic ethers were constructed via RCM reaction of enol ethers, allylic ethers, or alkynyl ethers. More recently, they have developed an efficient and flexible two-directional strategy for the construction of trans-fused polyether systems (Scheme 24). Tricyclic ethers, containing rings of various sizes, were prepared in moderate to excellent yield by two-directional double RCM reaction of substrates containing combinations of enol, allylic and alkynyl ethers.

Scheme 24
Clark and co-workers utilized their developed two-directional strategy for the synthesis of the A-E ring system 147 of CTX3C (4) (Scheme 25). Preparation of the cyclization precursor 142 commenced with conversion of known alcohol 140 into allyl ether 141. Following cleavage of the di-tert-butyldisilane group, the resultant diol was converted in five steps to the required double RCM precursor 142. Simultaneous diene and enyne RCM reaction upon treatment of 142 with Grubbs second generation catalyst 148, constructed both the A- and C-rings of the target system. Formation of the D-ring began with selective epoxidation of the electron-rich enol ether 143. Regioselective reduction of the resulting epoxide provided alcohol 144. Alkylation of alcohol 144 furnished RCM precursor 145. Treatment of enone 145 with catalyst 148 provided tetracycle 146. The E-ring was then introduced via the enone formation and RCM sequence to afford the A-E ring system 147 of CTX3C (4).

Scheme 25

a) 148 (10 mol%), CH$_2$CH$_2$, PhMe, 70 ºC, 58%; b) 1. DMDO, CH$_2$Cl$_2$, 0 ºC; 2. BF$_3$·Et$_2$O, Et$_3$SiH, MeCN, −40 ºC, 71% (2 steps); c) 1. NaH, ClCH$_2$COCHPh$_3$, TBAI, THF, reflux; 2. HCHO aq., Et$_2$O, 56% (2 steps); d) 148 (5 mol%), CH$_2$Cl$_2$, reflux, 70%.
3.0 Double RCM

3.1 Olefin Metathesis

The word metathesis is derived from the Greek words meta (change) and tithenai (to place), and literally means to transpose. Olefin metathesis was discovered in the mid-1950s by workers at DuPont, Standard Oil of Indiana and Phillips Petroleum during their investigations into Ziegler−Natta polymerization catalysis. Olefin metathesis is a catalytic process where two alkenes undergo bond reorganization in the presence of metal carbene complexes, resulting in the redistribution of the alkene moieties (Scheme 26).

![Scheme 26](image)

Olefin metathesis represents a powerful transformation in chemical synthesis. Over the past two decades it has attracted a vast amount of interest from researchers in both industry and academia. The importance of olefin metathesis was recognised in 2005 when Chauvin, Grubbs and Shrock were awarded the Nobel Prize in Chemistry “for the development of the metathesis method in organic synthesis”.

Olefin metathesis can be extended to different π-systems and has many applications: these include ring-opening metathesis polymerisation (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis (ADMET), cross-metathesis (CM), ring-closing enyne metathesis (RCEYM) and ring-closing alkyne metathesis (RCAM) (Scheme 27).
3.2 Olefin Metathesis Mechanism

The initial metathesis mechanism proposed by Calderon involved the pair-wise exchange of alkylidenes through a ‘quasicyclobutane’ mechanism (Scheme 28). In this mechanism, two olefins coordinate to the metal centre and exchange alkylidene groups through a symmetrical intermediate. With a few assumptions, this mechanism can account for outcomes observed in most of the basic metathesis transformations.

A later mechanism proposed by Chauvin was found to be more consistent with the experimental evidence, and even today remains the generally accepted metathesis mechanism (Scheme 29). The proposed mechanism is believed to occur via a metallocyclobutane intermediate through alternating [2+2] cycloadditions and cycloreversions.
The first step in the catalytic cycle is the formation of metallocyclobutane C via a [2+2] cycloaddition reaction between olefin B and the transition metal alkylidene complex A. This metallocycle then undergoes a [2+2] cycloreversion reaction to liberate ethene D and furnish the metal carbene E. A second [2+2] cycloaddition reaction between metal carbene E and olefin F provided metallocycle G. A further [2+2] cycloreversion reaction liberates alkene H; complex A is regenerated and re-enters the catalytic cycle.

Due to the reversible nature of the individual steps in the catalytic cycle, an equilibrium mixture of olefins is obtained. In order to make metathesis reactions productive in preparative terms, the equilibrium must be shifted in favour of the desired product.\textsuperscript{82} In the case of RCM, the reaction is entropically driven as the alkene substrate is transformed into two products. Furthermore, if one of these two products is volatile, the cycloreversion step becomes irreversible. The substitution pattern of the alkene also proves to be an important factor because it dictates the kinetics of the reaction. In general, the more substituted the alkene, the less reactive it is.\textsuperscript{85}
3.3 Catalysts

From the early discovery of Ta-based catalysts to the present-day N-heterocyclic carbene (NHC)-based catalysts, the design of metathesis catalysts has undergone a radical evolution. At present, two main types of catalyst are in practical use. The molybdenum catalyst 149, developed by Schrock and co-workers, along with ruthenium complexes 61 and 148, developed by Grubbs and co-workers, have been crucial to the expansion of metathesis as a general method in organic synthesis (Figure 12).

![Catalysts diagram](image)

Figure 12

Molybdenum catalyst 149 is highly reactive towards a broad range of substrates and numerous derivatives are available with various steric and electronic modifications. The drawbacks of the molybdenum-based catalysts are their poor functional group tolerance, along with their high sensitivity towards air, moisture and any impurities present in the solvent.

Ruthenium catalysts 61 and 148 have received a great deal of attention due to their excellent functional group tolerance combined with their significant stability towards both air and moisture. They can both be handled without the use of a glove box or Schlenk techniques. In recent years, Hoveyda and co-workers have developed a series of improved versions of Grubbs catalysts e.g. 150. These catalysts have been shown to display longer lifetimes, are reusable and, in cases where chiral ligands have been incorporated, show good enantioselectivity.
3.4 Double RCM

Over the years, the RCM reaction has been employed for the construction of numerous complex cyclic compounds. Recently, several applications of double RCM reactions of tetraenes to furnish the corresponding cyclic systems have been reported. Double RCM provides an attractive strategy as it facilitates the rapid construction of various polycyclic systems.

3.4.1 Synthesis of Fused Bicyclic Compounds via Double RCM

Lautens and co-workers became interested in using RCM methodology as a key step in their projected total synthesis of the HMG CoA reductase inhibitor (+)-mevinolin (153) (Scheme 30).\(^9\) It was proposed that a diastereoselective double RCM strategy involving 151, followed by an alkene selective sigmatropic rearrangement of 152, would provide convenient access to the carbon skeleton of the hexahyronaphthalene portion of (+)-mevinolin (153).\(^9\)

![Scheme 30](image)

Initial studies into the diastereoselective double RCM reaction were performed using unsubstituted tetraenes (Scheme 31). By analogy to fully saturated decalin systems, it was anticipated that the trans-fused decalins would be thermodynamically preferred. Treatment of tetraene 154 with Grubbs first generation catalyst 61 afforded a 1:2.8 mixture of diastereomers in favour of the trans-decalin 156. When tetraene 155 was treated with catalyst 61 under an atmosphere of ethylene, an 8:1 mixture of diastereomers was formed with the cis-decalin 157 now predominanting. Computational studies suggested that the formation of the cis-decalin was a kinetic outcome, and that at least one of
the steps in the reaction sequence prior to the final bond formation was irreversible.\textsuperscript{90} The diastereoselective double RCM strategy employed by Lautens and co-workers has provided access to a novel class of bicyclic diallylic alcohols and ethers.

Ma and co-workers investigated the construction of bicyclic pyrrolizidine, indolizidine and quinolizidine alkaloid skeletons \textit{via} a double RCM protocol.\textsuperscript{92} These particular alkaloid skeletons are found in several natural products.\textsuperscript{93} The proposed strategy relied upon the control of the RCM mode (\textit{ab/cd} vs \textit{ac/bd}) to provide the targeted fused bicycle 159 (Scheme 32).

Treatment of 161\textsubscript{a} and 161\textsubscript{b} with ruthenium catalyst 61 afforded a mixture of \textit{mode-ab/cd} and \textit{mode-ac/bd} products in favour of the dumbell-type products 163 (Table 2). Reaction of 161\textsubscript{c} under the same conditions furnished the corresponding products with a ratio of 162\textsubscript{c}:163\textsubscript{c} as high as 21:1 in favour of
the desired fused product. Interestingly, it was noted that reaction of 161d (with the methyl group in the terminal position of the carbon-carbon double bond), afforded fused bicycle 162d as the only product, indicating a substituent effect on the selectivity of cyclization. This reaction was extended to the synthesis of substituted 6,6-bicyclic lactam 162e.

![Diagram of the reaction]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Result</th>
<th>Table 2&lt;sup&gt;92&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>161a (R'&lt;Me, R''=R''')</td>
<td>64% (162a:163a, 1:3.6)</td>
<td></td>
</tr>
<tr>
<td>161b (R'= n-Pr, R''=R''')</td>
<td>41% (162b:163b, 1:3.8)</td>
<td></td>
</tr>
<tr>
<td>161c (R'=R''=R'''')</td>
<td>88% (162c:163c, 21:1)</td>
<td></td>
</tr>
<tr>
<td>161d (R'=R''=H R'''=Me)</td>
<td>86% (162d)</td>
<td></td>
</tr>
<tr>
<td>161e (R'=R''=H R'''=Me)</td>
<td>43% (162e)</td>
<td></td>
</tr>
</tbody>
</table>

Ma and co-workers have developed an efficient double RCM strategy for the construction of the target alkaloid skeletons. Reaction selectivity was tuned by the electronic and steric effects of the substituents on the N-containing tetraenes.

### 3.4.2 Synthesis of Spirocyclic Compounds via Double RCM

Harrity and co-workers employed a double RCM strategy for the novel construction of spirocyclic compounds such as 165. Tetraene 164 can undergo double RCM via two modes to afford two products (Scheme 33). The desired spirocyclization reaction would require selective metathesis of tetraene 164 through mode a to afford spirocycle 165, whereas monocyclic product 166 would arise from cyclization through mode b.
In order to establish the selectivity of *mode a* cyclization over *mode b*, model substrate 167 was prepared and its behaviour upon treatment with ruthenium catalyst 61 was investigated (Scheme 34). It was found that 5-membered ring cyclization proceeded with complete selectivity to afford dihydrofuran 168 with no detectable quantity of the acetal 169.\(^{94}\)

The double metathesis methodology was then applied to a range of tetraene precursors (Table 3).\(^{94}\) The spirocyclic carbocycles 171 and 173 were both isolated in excellent yield from their corresponding tetraene precursors. Spiroacetal 175 was readily assembled from 174 under mild conditions. Interestingly, acetal 175 rapidly decomposed upon treatment with catalytic \(p\)-toluenesulfonic acid at room temperature. This result implies that functionalised [4,4]-spiroacetals such as 175 cannot be accessed from the corresponding open chain ketone or acetal using traditional acid-catalysed reactions.\(^{95}\) The butenolide 177 was also successfully synthesised using the double RCM methodology.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate 170" /></td>
<td><img src="image2.png" alt="Product 171" /></td>
<td>98%</td>
</tr>
<tr>
<td><img src="image3.png" alt="Substrate 172" /></td>
<td><img src="image4.png" alt="Product 173" /></td>
<td>92%</td>
</tr>
<tr>
<td><img src="image5.png" alt="Substrate 174" /></td>
<td><img src="image6.png" alt="Product 175" /></td>
<td>90%</td>
</tr>
<tr>
<td><img src="image7.png" alt="Substrate 176" /></td>
<td><img src="image8.png" alt="Product 177" /></td>
<td>62%</td>
</tr>
</tbody>
</table>

<sup>a</sup> reaction conditions: 61 (5—15 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 25—40ºC.

Table 3<sup>94</sup>

The double RCM strategy has also been employed for the diastereoselective synthesis of selected spirocycles.<sup>96</sup> In 2000, Wallace and co-workers reported the first diastereoselective double RCM reaction to afford a spirocyclic target.<sup>97</sup> While investigating the development of selective NK-1 receptor antagonists, a route to compounds with the general structure 178 was required. It was envisioned that a double RCM reaction of tetraene 180 would afford the desired spirocyclic system 179 (Scheme 35).

![Scheme 35](image9.png)
A variety of N-tosyl protected metathesis precursors were prepared from commercially available amino acid esters (Table 4). In all cases, the easily separable spirocycles 182a-d and 183a-d were isolated in good yield. The diastereoselectivity of the double RCM reaction was strongly in favour of the required 5R,6S-isomers 182a-d, and appeared to be unaffected by the identity of alkyl substituent.

![Chemical structure](image)

a) 61 (5–7 mol%), CHCl₃, 20 ºC.

<table>
<thead>
<tr>
<th>Tetraene</th>
<th>R</th>
<th>Yield</th>
<th>Diastereoselectivity¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>181a</td>
<td>Me</td>
<td>74%</td>
<td>92%</td>
</tr>
<tr>
<td>181b</td>
<td>i-Pr</td>
<td>84%</td>
<td>92%</td>
</tr>
<tr>
<td>181c</td>
<td>i-Bu</td>
<td>76%</td>
<td>92%</td>
</tr>
<tr>
<td>181d</td>
<td>CH₂Ph</td>
<td>87%</td>
<td>92%</td>
</tr>
</tbody>
</table>

¹Isomer ratio determined by HPLC analysis

Table 4⁹⁷

Following their successful synthesis of spirocycles 182a-d, Wallace and co-workers turned their attention to the synthesis of the selective NK-1 receptor antagonist 1-oxo-7-azaspirodecane 187 (Scheme 36).⁹⁸ The metathesis precursor 185 was synthesised in three steps from the commercially available phenylglycine ester (184). The key double RCM reaction of tetraene 185 proceeded smoothly upon treatment with ruthenium catalyst 61. Diastereomers 186 and 5-epi-186 were isolated in good yield and with 70% diastereoselectivity in favour of the desired isomer 186. Selective functionalization of 186 furnished the target 187 in three further steps.
3.4.3 Synthesis of Natural Products via Double RCM

Martin and co-workers have pioneered the application of RCM to the synthesis of nitrogen heterocycles and a variety of alkaloid natural products.\textsuperscript{99} Their concise total synthesis of the pentacyclic (±)-pseudotabersonine (188) employed a double RCM reaction to facilitate the rapid construction of the carbon skeleton of this natural product (Figure 13).\textsuperscript{100}

The metathesis precursor 190 was synthesised in six steps from the commercially available indole aldehyde 189 (Scheme 37).\textsuperscript{100} The key double RCM reaction of the tetraene 190 proceeded smoothly upon treatment with ruthenium catalyst 150 to afford an inseparable mixture of the cis- and trans-fused tetracycles 191 and 192. Catalytic hydrogenation of the crude mixture resulted in regioselective reduction of the less substituted alkene.
Subsequent removal of the silyl ether provided tetracycles 193 and 194 as a separable mixture in moderate yield over the three steps. Conversion of 194 into the pentacyclic intermediate 195 was achieved through the use of an N-deprotection/O-sulfonylation and cyclization process first reported by Bosch and co-workers. Deprotonation of 195 followed by selective acylation with Mander’s reagent furnished (±)-pseudotabersonine (188).

![Chemical structures](image)

(±)-pseudotabersonine 188

a) 150 (5 mol%), PhMe, 100 ºC, dr 7:10; b) 1. 10% PtO₂, EtOH, H₂; 2. HCl, MeOH, 193 = 26%, 194 = 44% (3 steps); c) KOTBu, DME/THF, −20 to −5 ºC, 66%; d) LDA, THF, −78 to −20 ºC; then NCO₂Me, −78 ºC, 61%.

Scheme 37
Norcross and co-workers have employed double RCM methodology for the synthesis of several lupine alkaloids. The lupine alkaloids constitute a structurally diverse group of natural products found in numerous varieties of leguminous plants and trees. The sparteine subgroup of lupine alkaloids are characterized by a common 3,11-diazatetracyclo[7.7.1.0.0]heptadecane ring system (Figure 14). All three targets were synthesised from the common bisimide intermediate 196.

The synthesis of (±)-α-isosparteine 197 began with the addition of excess allylmagnesium bromide to bisimide 196 to generate tetraene 200 (Scheme 38). Double RCM of tetraene 200 with ruthenium catalyst 61 proceeded smoothly to furnish the tetracyclic sparteine congener 201. Completion of the total synthesis required hydrogenation followed by deoxygenation to afford (±)-α-isosparteine 197.
Alkaloids (±)-β-isosparteine 198 and (±)-sparteine 199 were synthesised in a similar manner from tetraene precursors 202 and 203 respectively (Scheme 39).
Clark and co-workers have utilized the double RCM methodology in their two-directional synthesis of selected polycyclic ether fragments (see Ch 1. § 2.4.1).\textsuperscript{77, 106} In 2005, they reported the rapid and efficient two-directional construction of the F-J ring system 214 of the gambieric acids 204–207 (Figure 15).\textsuperscript{106a} The gambieric acids are marine polyethers (see Ch 1. § 1.2) that exhibit potent and selective antifungal activity.\textsuperscript{107}

The synthesis of the pentacyclic target 214 began from the commercially available tri-O-acetyl-d-glucal 208 (Scheme 40). Diol 209 was prepared from 208 in ten synthetic steps and with an overall yield of 36%. Diol 209 was then converted into the corresponding bis(alkynyl ether) 210 using a one-pot alkynylation procedure developed by Greene and co-workers.\textsuperscript{108} The first metathesis precursor 211 was prepared from 210 using sequential carbocupration reactions.\textsuperscript{109} When bis(enol ether) 211 was treated with Grubbs second generation catalyst 148, tricyclic product 212 was obtained in excellent yield. Following the double hydroboration of 212, a series of functional group manipulations allowed for elaboration to the second metathesis precursor 213. The final crucial double RCM reaction to construct the required nine- and six-membered rings proceeded smoothly to afford the target F-J ring system 214. The synthesis of the pentacyclic F-J ring system 214 of the gambieric acids highlighted the advantages of employing a two-directional double RCM strategy for the synthesis of polyether natural products.

![Figure 15](image_url)
a) KH, Cl₂CCHCl. THF, 0 ºC; then n-BuLi, Et₂O, −40 to −78 ºC, 88%;
b) PMBO(CH₂)₃MgBr, CuBr, LiBr, THF, −95 to −78 ºC, 85%;
c) 148 (10 mol%), PhMe, 70 ºC, 89%;
d) 148 (10 mol%), PhMe, 80 ºC, 60%.

Scheme 40

Feldman and co-workers have also exploited a two-directional strategy that incorporates the double RCM methodology for the synthesis of a targeted natural product.¹¹⁰ Their approach to the central lomaiviticin A aglycone core 216 utilized a sequence involving double Ireland-Claisen ester enolate rearrangement and double RCM to deliver the central bis-cyclohexenone region (Figure 16). Lomaiviticin A (215) is a member of a small class of marine natural products which are characterized by the presence of the unusual diazoparaquinone moiety.¹¹¹
The synthesis of central bis-cyclohexenone region 222 began with the preparation of the Claisen rearrangement precursor 218 from chiral propargyl alcohol 217 (Scheme 41). Double Ireland-Claisen ester enolate rearrangement of dienyl glycolate 218 provided diacid 219 which possessed the desired stereochemistry.\textsuperscript{112} Elaboration of 219 proceeded via two-directional chain extension of the carboxylic acid units to afford the allyl ketones required for the double RCM sequence. Bis-cyclohexene product 221 was obtained in good yield upon the treatment of metathesis precursor 220 with Grubbs second generation catalyst 148. The bis-cyclohexene 221 was converted into the desired bis-cyclohexenone 222 following a short synthetic sequence. Feldman and co-workers successfully implemented a two-directional double RCM strategy for the completion of the core bicyclic system 222 of lomaiviticin A (215).
3.5 Summary

Olefin metathesis has emerged as one of the most powerful strategies for carbon-carbon bond construction. The development of well-defined catalysts which are able to combine high activity, durability and excellent tolerance towards a wide range of functional groups has revolutionised the field. Over the years, RCM has proven to be the most important olefin metathesis reaction. This methodology has been applied to the synthesis of numerous complex natural products. The development of the double RCM reaction has enabled the rapid construction of various structurally complex polycyclic systems.
Chapter 2: Results and Discussion
Chapter 2: Results and Discussion

1.0 Introduction

Previous work within the group had established an efficient two-directional strategy for the synthesis of various polycyclic ether systems (see Ch 1. § 2.4.1).\textsuperscript{76} This two-directional methodology was employed for the synthesis of the A-E ring system \textbf{147} found in CTX3C (4).\textsuperscript{77} It was proposed that a similar two-directional strategy could be developed for the construction of the IJK-tricyclic core \textbf{224} of the H-M ring system \textbf{223} of CTX3C (4). In order to allow for comprehensive investigation of the chemistry required to construct the IJK-tricyclic core \textbf{224}, two model systems were designed (Scheme 42). Both model systems were derived from tri-O-acetyl-d-glucal \textbf{208}, which was to provide the J-ring in each model compound. Our next challenge was to design a suitable two-directional strategy to the target IJK-tricycle \textbf{224}. Both model syntheses shared several common steps, which would be translated into a suitable two-directional approach to the tricyclic target \textbf{224}.

\begin{center}
\textbf{Scheme 42}
\end{center}
2.0 Synthesis of the IJ-model 225

In order to investigate the chemistry required for the construction and functionalization of the eight-membered I-ring, the IJ-model system 225 was designed.

2.1 Retrosynthesis of the IJ-model 225

Retrosynthetic analysis of the IJ-model 225 is shown below (Scheme 43). Removal of the methyl group from ketone 225 implies conjugate addition to enone 227 to install this pendant methyl group in the forward direction. Disconnection of the allyl side chain to give 228 followed by scission of the alkene provides diene 229 and implies an RCM reaction in the forward direction. Removal of the ether linkage affords the secondary alcohol 230 which could be readily prepared from enol ether 231. Deprotection affords the corresponding diol, which can be synthesised from commercially available tri-O-acetyl-D-glucal 208.113
2.2 Synthesis of Alcohol 230

The synthetic route toward the IJ-model system 225 began from commercially available tri-\(\text{O-}\)acetyl-\(\text{D-}\)glucal 208 (Scheme 44). Treatment with methanol in the presence of boron trifluoride diethyl etherate delivered the mixed acetal 232 by Ferrier rearrangement.\(^{113}\) Displacement of the allylic methoxy group followed by simultaneous removal of the two acetate groups was achieved through reaction of acetal 232 with lithium aluminium hydride.\(^{114}\) The diol 233 was obtained in high yield over the two steps.

\[
\begin{align*}
\text{AcO} & \quad \text{H} \quad \text{OAc} \\
\text{O} & \quad \text{H} \quad \text{OAc} \\
208 & \quad \leftarrow \quad a
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{OAc} \\
\text{H} & \quad \text{OAc} \\
232 & \quad \text{b}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{OH} \\
233 & \quad \text{a) BF}_3\cdot\text{Et}_2\text{O, MeOH, CH}_2\text{Cl}_2, \text{rt; b) LiAlH}_4, \text{dioxane, reflux, 81\% (2 steps).}
\end{align*}
\]

Scheme 44

2.2.1 Protection of Diol 233

Following the isolation of enol ether 233, our next goal was the protection of the 1,3-diol. A variety of protecting group strategies were considered at this stage.

\textit{TBS-group Protection Strategy}

The first protection strategy investigated was the use of TBS-groups to protect the 1,3-diol. One benefit of this protection protocol is that it allows selective deprotection of the primary alcohol, if this should be required. TBS-groups were installed to afford cyclic enol ether 234 in 80\% yield (Scheme 45). Epoxidation of the enol ether double bond using a preformed acetone solution of dimethyl dioxirane provided a diastereomeric mixture of the epoxides 235 (4:1 mixture of diastereomers).\(^{115}\)
Once isolated, epoxides 235 were treated directly with allylmagnesium chloride with the aim of affording the corresponding alcohol. Numerous attempts at this alkylation step yielded only recovered starting material or decomposition products. Previous work carried out within the group has shown that the alkylation of epoxides 235 was a challenging step, with the only successful attempt giving a 9% yield of alcohol 236.\textsuperscript{116} A variety of reaction conditions were explored. It was found that treatment of epoxides 235 with a freshly prepared solution of allylmagnesium bromide afforded alcohol 236 in good yield with a diastereomeric ratio > 20:1 (Scheme 46).

Although trans-diaxial ring opening of one diastereomer of epoxides 235 led to alcohol 236, the remaining starting material afforded only decomposition products. The stereochemistry of alcohol 236 was confirmed through \textsuperscript{1}H NMR NOE analysis (see Appendix A). Unfortunately, the stereochemistry observed in alcohol 236 was not that required for the formation of the target IJ-model system 225. The highlighted hydrogens display a trans-relationship in alcohol 236 while in the target system 225 there is a cis-relationship across the polycyclic ether (Scheme 46).
Inversion of stereochemistry at the stereocentres bearing the alcohol and allyl functionalities was necessary in order to introduce the desired stereochemistry. It was envisioned that inversion to give the required stereochemistry could be accomplished through a simple three-step sequence (Scheme 47). Oxidation of alcohol 236, followed by epimerisation of the allyl group to the more stable equatorial product would afford ketone 238. Reduction of 238 would complete the sequence to provide the desired alcohol 239.

Scheme 47

The first step in the sequence, oxidation of alcohol 236, proved unexpectedly challenging. A wide selection of reaction conditions were screened for the oxidation of the TBS-protected alcohol 236 (Table 5). The use of an activated DMSO reagent (entries 1–3) was unsuccessful. Chromium oxidation reagents were also investigated with no success (entries 4–6) and the use of a hypervalent iodine reagent returned only starting material (entries 7). As a consequence of the failure to identify suitable conditions for the oxidation of alcohol 236, it was decided that other protecting group strategies would be investigated.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Temperature</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COCl₂, DMSO, CH₂Cl₂</td>
<td>-78 ºC</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>COCl₂, DMSO, CH₂Cl₂</td>
<td>-45 ºC</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>SO₃·py, Et₃N, DMSO, CH₂Cl₂</td>
<td>0 ºC</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>PCC, CH₂Cl₂</td>
<td>rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>PDC, CH₂Cl₂</td>
<td>rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>PDC, CH₂Cl₂</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>DMP, CH₂Cl₂</td>
<td>0 ºC</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>TEMPO, PhI(OAc)₂, CH₂Cl₂</td>
<td>rt</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

*a* reaction progress followed by NMR.

Table 5

**Acetal Protection Strategy**

The next protection strategy to be investigated involved protection of diol 233 using either a benzylidene or a *p*-methoxybenzylidene acetal. As with the TBS-protection strategy, the use of a *p*-methoxybenzylidene acetal would allow for the selective deprotection of the primary alcohol if required.¹¹⁷ Both acetal protecting groups were successfully installed to afford bicyclic enol ethers 240 and 241 (Scheme 48).¹¹⁸

![Scheme 48](image)

a) benzaldehyde dimethylacetal, CSA (5 mol%), DMF, rt, 54%; b) *p*-anisaldehyde dimethylacetal, PPTS (20 mol%), CH₃CN, 0 ºC to rt, 59%.
Following the synthesis of compounds 240 and 241, in moderate but acceptable yields, the next step was epoxidation using dimethyl dioxirane. Unfortunately, attempted epoxidation of the bicyclic enol ethers 240 and 241 under these reaction conditions resulted in decomposition of the starting material (Scheme 49). It is possible that the observed decomposition reaction might arise from oxidation at the activated benzylic position within the acetal protecting group.

Due to the difficulties encountered during the attempted epoxidation of both acetal-protected enol ethers, no further work was undertaken on these compounds.

**Di-tert-butyldisiloxane Protection Strategy**

This strategy explored the suitability of employing the di-tert-butyldisiloxane group for the protection of diol 233. Upon reaction with di-tert-butyldisilylbis(trifluoromethanesulfonate), diol 233 was protected as the corresponding bicyclic enol ether 231 in 94% yield (Scheme 50). Epoxidation of the enol ether with dimethyl dioxirane afforded a diastereomeric mixture of the epoxides 246 (1.2:1 mixture of diastereomers). It was discovered that in order to avoid epoxide decomposition, the reaction work-up was very important. Once the reaction had reached completion it was necessary to dry the reaction mixture with magnesium sulfate, and then concentrate the solution under reduced pressure at 4 °C. Following this work-up protocol, a diastereomeric mixture of epoxides 246 was obtained in quantitative yield (1.2:1 mixture of diastereomers).
The epoxides 246 were treated directly with allylmagnesium chloride to provide alcohols 248 as a mixture of diastereomers (Scheme 51). Purification of this mixture proved to be very difficult. However, a small amount of the main diastereomer was isolated and subjected to NMR analysis. Through $^1$H NMR NOE correlations between CH-C2, CH-C5 and CH$_2$-C7 (see Appendix A), the main diastereomer was confirmed to be alcohol 247. As was the case with alcohol 236, alcohol 247 displayed the undesired trans-stereochemistry across the polycyclic ether (Figure 17).

The decision was made to take the mixture on to the next stage rather than optimising the purification of alcohols 248 (Scheme 51). Oxidation of the crude mixture of alcohols 248 under Parikh-Doering conditions afforded ketones 249 as a 2.3:1 mixture of diastereomers.$^{119}$
The next step was epimerisation of ketones 249 to give the desired equatorial configuration at the carbon bearing the allyl group. The use of either sodium hydroxide or potassium carbonate resulted in decomposition of the starting material (entries 1 and 2) (Table 6). When DBU was employed as the base at room temperature, 0 ºC or at reflux, a mixture of recovered starting material and decomposition products was obtained (entries 3–5). It was found that performing the reaction in the dark had a surprising effect on the outcome of the reaction (entry 6). The exact reasons for the detrimental effect of light on the reaction remain unclear. Performing the reaction using DBU at room temperature with the reaction vessel carefully covered to exclude light resulted in a reproducible reaction yield of 60%.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH, EtOH</td>
<td>rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃, MeOH</td>
<td>rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>DBU, PhMe</td>
<td>rt</td>
<td>35% SM recovered/decomposition</td>
</tr>
<tr>
<td>4</td>
<td>DBU, PhMe</td>
<td>0 °C to rt</td>
<td>43% SM recovered/decomposition</td>
</tr>
<tr>
<td>5</td>
<td>DBU, PhMe</td>
<td>reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>DBU, PhMe, in the dark</td>
<td>rt</td>
<td>60% yield</td>
</tr>
</tbody>
</table>

Table 6

With the correct stereochemistry installed in ketone 250, the next step was reduction to the desired alcohol 251 (Scheme 52). Pleasingly, treatment with sodium borohydride afforded 251 in high yield with a diastereomeric ratio of 10:1. The stereochemistry of alcohol 251 was confirmed by comparison to the known literature data,¹²⁰ along with ¹H NMR NOE correlations between CH-C1, CH-C5 and CH₂-C₃ax (see Appendix A).

Scheme 52

a) NaBH₄, CH₂Cl₂:MeOH (1:1), −78 °C, 88%.
2.3 Synthesis of Enone 228

With the correct stereochemistry installed around the J-ring, the next challenge was construction of the eight-membered I-ring utilizing an enone/RCM protocol.

2.3.1 Clark’s Approach to Cyclic Enones

Cossy and co-workers have developed an efficient route to six-, seven-, and eight-membered 3-oxo oxacycloalkenes 255 from the corresponding α-alkoxy enones 254 (Scheme 50). It was ascertained that these enones could be synthesised via the corresponding stabilized phosphoranes 253. Alkylation using sodium hydride with triphenylchloroacetonylphosphorane afforded the required phosphoranes 253 in moderate to high yields. These compounds were then converted into the desired α-alkoxy enones 254 upon condensation with formaldehyde.

\[
\text{252} \xrightarrow{\text{a}} \text{253} \xrightarrow{\text{b}} \text{254} \xrightarrow{\text{c}} \text{255}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>254</th>
<th>148 (mol%)</th>
<th>Yield of 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n = 0, R^1 = R^2 = H</td>
<td>2.5</td>
<td>69%</td>
</tr>
<tr>
<td>2</td>
<td>n = 1, R^1 = R^2 = H</td>
<td>15</td>
<td>58%</td>
</tr>
<tr>
<td>3</td>
<td>n = 2, R^1 = R^2 = H</td>
<td>10</td>
<td>66%</td>
</tr>
</tbody>
</table>

a) NaH, ClCH_2COCHPPh_3, THF, rt or reflux, 48-94% (n=0–2); b) CH_3O aq., H_2O/Et_2O, rt, 49–73% (n=0–2); c) 148, CH_2Cl_2, reflux.

Scheme 53\textsuperscript{121}
Treatment of α-alkoxy enones 254 with Grubbs second-generation catalyst 148 allowed for the isolation of six-, seven-, and eight-membered cyclic enones 255 in good yield. It is worth noting the success of this protocol in the formation of eight-membered rings which are normally difficult to synthesize.

Clark and co-workers have previously utilized Cossy’s approach to cyclic enones in the synthesis of several polycyclic ether targets.77, 106a Cossy’s methodology was incorporated into the synthetic routes used to prepare the A-E ring system 147 of CTX3C (4),77 and the fused tetracyclic polyether core 256 of hemibrevetoxin B (9) (Figure 18).106b

![Figure 18](image)

Both of the seven-membered rings in the tetracyclic polyether core 256 of hemibrevetoxin B (9) were constructed using a two-step sequence of enone formation and RCM reaction (Scheme 54). The alcohol 257 was alkylated using triphenylchloroacetonylphosphorane and condensation of the resulting phosphorane with formaldehyde then provided enone 258. Construction of the seven-membered ring was completed upon treatment of 258 with ruthenium catalyst 148. The second seven-membered ring was constructed by employing the same sequence of enone formation and subsequent RCM reaction to afford tetracycle 256.106b
Scheme 54

It is clear that this methodology provides a powerful tool that can be used to access various polyether systems. This efficient two-stage enone formation and RCM reaction sequence was investigated for the construction of the targeted eight-membered l-ring.
2.3.2 Initial Strategy for the Synthesis Enone 228

Alkylation of alcohol 229 with triphenylchloroacetonylphosphorane afforded the corresponding stabilized phosphorane 262 (Scheme 55). Subsequent condensation with formaldehyde yielded enone 229.

Unfortunately, low yields were observed for the transformation of alcohol 230 into enone 229 (15–31%, two steps). It was believed that the problem lay in the Wittig reaction between phosphorane 262 with aqueous formaldehyde. The RCM reaction was then attempted using the small amount material that was isolated. Treatment of enone 229 with Grubbs’ second-generation catalyst 148 resulted in the recovery of starting material without product formation. Attempts to achieve the RCM reaction by varying the metathesis catalyst employed, the catalyst loading or reaction concentration proved ineffective.

It has been reported that polar groups such as ethers, ketones and esters can act to position the reacting sites within the co-ordination sphere of the metal (A). It was proposed that this directing behaviour favours ring closure (B). However, if complexation confers a high degree of stability, the catalyst can become trapped in the form of an unproductive complex (C) (Figure 19).
This unproductive complexation between substrate and catalyst may be to blame for the lack of ring closure observed upon treatment of enone 229 with the Grubbs second-generation catalyst 148. The utilization of a Lewis acid additive, such as Ti(O-i-Pr)$_4$, to overcome unwanted complexation between the polar group and metal centre is well documented in the literature. However, previous studies within the group have found that the optimisation of reaction conditions with these additives can prove challenging. For this reason, alternative reaction conditions were investigated.

The effect of allylic substituents in RCM reactions has been well studied. It was widely believed that an allylic alcohol adversely effects metathesis reactions that involve the adjacent double bond. However, recent reports suggest that this functionality is not only tolerated, but may even assist the metathesis reaction (Scheme 56).

\[
\begin{array}{ccc}
\text{OH} & \text{a} & \text{OH} \\
\text{263} & \rightarrow & \text{264} \\
\end{array}
\]

a) 148 (2.5 mol%), CH$_2$Cl$_2$, rt, 87%.

Scheme 56$^{128c}$
Construction of eight-membered rings by RCM in substrates containing an unprotected allylic alcohol has been achieved in the synthesis of several polyether fragments.\textsuperscript{49, 129} Oishi and co-workers demonstrated the viability of such ring construction in the synthesis of the F-J ring system 266 of yessotoxin.\textsuperscript{129} In this case, treatment of diene 265 with ruthenium catalyst 148 afforded alcohol 266 in 68\% yield (Scheme 57).

Based on these reports, it was decided to reduce enone 229 to the corresponding diastereomeric alcohols 267 before attempting the RCM reaction. Luche reduction of enone 229 afforded alcohols 267 (1:1 mixture of diastereomers) (Scheme 58). To prevent the unwanted isomerisation of allylic alcohols to the corresponding ketones, the use of the more reactive metathesis catalysts, such as 150, was required.\textsuperscript{130} Pleasingly, treatment of 267 using Hoveyda-Grubbs second generation catalyst 150 effected ring closure to provide alcohols 268. It was observed that the concentration of the RCM reaction had a significant effect on the reaction yield: increasing the dilution by a factor of 10 almost doubled the yield obtained for the reaction. The hydroxyl group was oxidised upon treatment with Dess-Martin periodinane, to afford the target enone 228 in 82\% yield.
Subjection of enone 229 to the three-step Luche reduction, RCM and oxidation sequence delivered the target tricyclic enone 228 in good yield. However, the poor yield obtained for the formation of enone 229, the precursor required for this sequence, meant this approach was not a viable synthetic option. For this reason, other strategies were investigated.

2.3.3 Alternative Strategies for the Synthesis of Enone 228

**tert-Butyl Ester Strategy**

The first alternative strategy focussed on the formation of alcohols 267 from the corresponding tert-butyl ester 269 (Scheme 59). Treatment of alcohol 230 with tert-butyl bromoacetate afforded ester 269, which was then converted into aldehyde 270 upon DIBAL reduction. Direct treatment of aldehyde 270 with vinylmagnesium bromide afforded the required alcohols 267. Although this reaction sequence was effective on a small scale, it proved to be more challenging when performed on a large scale due to the unreliable nature of the esterification reaction.
The synthesis of desired enone \textbf{228} from the alcohols \textbf{267} can be achieved through a simple two-step sequence involving RCM reaction and subsequent oxidation, as had been demonstrated in the initial strategy (see Scheme 58).

\textit{Weinreb Amide Approach}

Another approach toward the synthesis of enone \textbf{228} was via the weinreb amide \textbf{271} (Scheme 60). Treatment of alcohol \textbf{230} with 2-bromo-N-methoxy-N-methylacetamide afforded \textbf{271}. Unfortunately, the synthesis of amide \textbf{271} proved to be problematic with a significant proportion of starting material being recovered from the reaction.
Modification of the Initial Wittig Strategy

As a consequence of the challenges encountered in both alternative strategies, it was decided to investigate the possibility of improving the initial Wittig sequence. It was believed that the problems with the initial strategy were encountered during the Wittig reaction of formaldehyde with the stabilized phosphorane 262 (see Scheme 55). The problems with the Wittig reaction were attributed to the aqueous conditions that resulted from the use of a 48% aqueous solution of formaldehyde. A selection of alternative aldehydes were considered.

Butyraldehyde was deemed to be a suitable alternative, with literature reports suggesting that the presence of a small alkyl chain should not interfere with the subsequent RCM reaction. Alcohol 230 was alkylated by sequential deprotonation using sodium hydride and treatment of the alkoxide with triphenylchloroacetonylphosphorane to afford phosphorane 262 (Scheme 61). Pleasingly, Wittig reaction between butyraldehyde and the stabilized phosphorane 262 afforded enone 272 in 86% yield over the two steps. This synthetic sequence provided reliable reaction yields.
Following the synthesis of 272, the next step was ring closure to form tricyclic enone 228. It was hoped that direct treatment of 272 with the Grubbs second-generation catalyst 148 would afford the target enone 228. However, as with enone 229, ring closure was not observed (Scheme 62). This result was not entirely unexpected due to the structural similarities between enones 229 and 272.

The problem was circumvented by the use of a three-step reduction, RCM and oxidation sequence (Scheme 63). Luche reduction of enone 272 afforded alcohols 273 (1:1 mixture of diastereomers). Treatment of 273 with the Hoveyda-Grubbs second generation catalyst 150 effected ring closure to afford alcohols 268 in excellent yield. Pleasingly, the substitution of butyraldehyde for formaldehyde did not have an adverse effect upon the outcome of the RCM
reaction. Finally, oxidation with Dess–Martin periodinane afforded target enone 228 in good yield.

![Scheme 63](image)

a) NaBH₄, CeCl₃·7H₂O, −78 ºC, 93%, dr 1:1; b) 150 (5 mol%), CH₂Cl₂, 0.001 M, 96%, dr 1:1; c) DMP, CH₂Cl₂, 0 ºC, 78%.

### 2.4 Functionalization of Enone 228

Completion of the IJ-model system 225 required functionalization of the eight-membered I-ring. This functionalization entailed the stereoselective incorporation of an allyl side chain followed by 1,4-conjugate addition (Figure 20).

![Figure 20](image)
Direct alkylation of enones is notoriously difficult to perform under standard conditions, but has been reported by Cossy and co-workers.\textsuperscript{121} Previous work performed in the group towards the use of these reaction conditions for the allylation of enone 274 has proved unsuccessful (Scheme 64).\textsuperscript{116}

Scheme 64\textsuperscript{116}

Tsuji and co-workers have reported the α-allylation of ketones and aldehydes via a decarboxylative palladium-catalyzed rearrangement.\textsuperscript{132} The proposed mechanism for this palladium-catalyzed rearrangement reaction is shown below (Scheme 65). Treatment of allyl enol carbonate 276 with a Pd\textsuperscript{0} source furnishes the corresponding π-allyl palladium complex 277. Decarboxylation of 277 affords intermediate 278. Alkylated product 279 is delivered upon attack of the electrophilic π-allyl complex by the nucleophilic enolate.\textsuperscript{133}

Scheme 65\textsuperscript{133}
Stoltz and co-workers reported the first catalytic enantioselective Tsuji allylation from allyl enol carbonate substrates. A screen of chiral ligands revealed that the phosphinooxazoline ligand (S)-tBu-PHOX (S)-282, a chelating P/N ligand, was especially effective in terms of both yield and enantioselectivity (Scheme 66). The mild and operationally straightforward reaction conditions allowed for the formation of quaternary stereocentres at the α-position in excellent yield with high enantiopurity. It is worth noting that the reaction displayed good tolerance to a variety of substituents and functional groups, as well as differing ring sizes.

Based on these results, enone 228 was converted to the corresponding allyl enol carbonate 283 (Scheme 67). It was known that Barbier-type conditions, in which enone 228 and allylchloroformate were cooled to −78 °C before addition of the base, were optimal for this reaction. When these conditions were employed, the carbonate 283 was obtained in 89% yield. The next step was the palladium-catalyzed rearrangement of 283. Initially, the reaction was performed using conditions previously optimised within the group. When a chiral ligand was not employed and Pd(PPh₃)₄ was selected as the Pd⁰ source, the alkylated enone 284 was isolated in 75% yield with a diastereomeric ratio of 1.8:1 in favour of the required diastereomer. Epimerisation of alkylated enone 284 with DBU improved the diastereomeric ratio from 1.8:1 to 5:1 in favour of the cis-diastereomer 227.
The use of the phosphinoxazoline \((S)-tBu-PHOX\) ligand \((S)-282\) in the rearrangement was then investigated. Treatment of allyl enol carbonate \(283\) with \(\text{Pd(PPh}_3)_4\) and \((S)-tBu-PHOX\) ligand \((S)-282\) afforded alkylated enone \(227\) in 85\% yield with a diastereomeric ratio of \(>20:1\) in favour of the desired \textit{cis}-diastereomer (Scheme 68). The absolute configuration at the newly created stereocentre was confirmed through \(^1\text{H}\) NMR NOE analysis (see Appendix A).

\begin{align*}
\text{a)} \quad \text{Pd(PPh}_3)_4 \ (10 \text{ mol\%}), \ (S)-tBu-PHOX \ (S)-282 \ (25 \text{ mol\%}), \ \text{THF, rt, 85\%, dr >20:1.}
\end{align*}
The successful preparation of the alkylated enone 227 meant that installation of the methyl group by 1,4-conjugate addition could be explored. Previous reports regarding similar polycyclic ether fragments had shown that the stereoselective introduction of a methyl group is possible (Scheme 69). Reaction of enone 285 with Me$_2$Cu(CN)Li$_2$ afforded the desired product 286 as a single isomer in good yield.

a) Me$_2$Cu(CN)Li$_2$, Et$_2$O, −78 ºC, 74%.

Scheme 69

The same reaction conditions were employed for the stereoselective installation of the methyl group to alkylated enone 227 (Scheme 70). Treatment of 227 with Me$_2$Cu(CN)Li$_2$ effected 1,4-conjugate addition to afford the targeted methylated product 225 in 89% yield. The stereochemistry of the methyl-bearing stereogenic centre was confirmed through $^1$H NMR NOE analysis (see Appendix A).

a) Me$_2$Cu(CN)Li$_2$, Et$_2$O, −78 ºC, 89%, dr >20:1.

Scheme 70
2.5 Summary

Alcohol 230 was synthesised from the commercially available tri-O-acetyl-D-glucal 208 in eight steps (Scheme 71). The di-tert-butylsiloxane group was identified as the optimal protecting group for this synthetic sequence. By employing an improved version of the initial Wittig strategy, enone 272 was obtained from alcohol 230 in two steps. Although the RCM reaction of enone 272 proved to be unsuccessful, RCM of the alcohols 273 provided a suitable route to the tricyclic enone 228. Pleasingly, it was found that enone 228 could be transformed into the desired IJ-model system 225. Side-chain introduction was accomplished by Tsuji alkylation and the secondary methyl group installed stereoselectively upon treatment of the resulting enone with Me₂Cu(CN)Li₂. Overall, the synthesis of the IJ-model system 225 was completed in sixteen steps from tri-O-acetyl-D-glucal 208. The synthesis of the IJ-model system 225 allowed the transformations required for the successful construction and functionalisation of the eight-membered I-ring to be tested.

![Scheme 71](image-url)
3.0 Synthesis of the JK-model 226

A second model system was designed in order to investigate the chemistry required for the construction and functionalization of the seven-membered K-ring.

3.1 Retrosynthesis of the JK-model 226

The retrosynthetic analysis of the JK-model 226 is shown below (Scheme 72). Disconnection of the hydroxyl group leads to ketone 287 and implies that the hydroxyketone functionality will be introduced by Rubottom oxidation in the forward synthesis. Subsequent retro 1,4-conjugate addition affords bicyclic enone 288. Removal of the allyl side chain and subsequent alkene disconnection provides diene 290 and implies an RCM reaction in the forward direction. Disconnection of the ether linkage affords the secondary alcohol 291. Alcohol 291 can be readily prepared in several synthetic steps tri-O-acetyl-d-glucal 208.
3.2 Synthesis of Alcohol 291

As before (see Ch 2. § 2.2), diol 233 was prepared from tri-O-acetyl-α-glucal 208 (see Scheme 44). Ferrier rearrangement followed by treatment with lithium aluminium hydride afforded diol 233 in good yield over the two steps. The next step was hydrogenation of the double bond to remove the labile enol ether. Treatment with a sub-stoichiometric amount of palladium on carbon under an atmosphere of hydrogen afforded diol 292 in excellent yield. Following the successful hydrogenation reaction, introduction of the required vinyl group was required. From diol 292, oxidation of the primary alcohol followed by Wittig methylenation with methyltriphenylphosphonium bromide was expected to afford alcohol 291 (Scheme 73).

![Scheme 73](image)

a) 10% Pd/C (5 mol%), EtOAc, H₂ (1 atm), rt, 94%.

The chemoselective oxidation of a primary alcohol in the presence of a secondary one was investigated. A N-oxoammonium salt based oxidation using a catalytic amount of (2,2,6,6-tetramethyl-1-piperidinyl)oxy (TEMPO) in conjunction with N-chlorosuccinimide (NCS) as the stoichiometric oxidant was reported to display the required degree of chemoselectivity. Unfortunately, when diol 292 was subjected to these reaction conditions, selective oxidation was not observed (Scheme 74).

![Scheme 74](image)

a) TEMPO, TBACl, NCS, CH₂Cl₂:NaHCO₃ aq.:K₂CO₃ aq. (2:1:1).
The unsuccessful chemoselective oxidation of diol 292 meant that an alternative protection/deprotection strategy was necessary. The TBS-protection of diol 292 proceeded smoothly to afford the corresponding cyclic ether 294 in excellent yield. Selective deprotection of the primary alcohol to afford 295 was achieved upon treatment of 294 with camphorsulfonic acid (Scheme 75).

![Scheme 75](image)

a) TBSCl, DMAP (20 mol%), imidazole, DMF, 0 ºC, 93%; b) CSA (30 mol%), CH\(_2\)Cl\(_2\):MeOH (1:1), 0 ºC, 89%.

Following preparation of alcohol 295, the vinyl group could be introduced. A two-step sequence of oxidation, followed by Wittig methylation was selected for this functional group modification (Scheme 76). Oxidation was performed under Parikh-Doering conditions to afford aldehyde 296. Subsequent Wittig reaction with methyltriphenylphosphonium bromide furnished alkene 297 in good yield over the two steps. Complete silyl ether cleavage upon treatment with camphorsulfonic acid then afforded the corresponding alcohol 291.

![Scheme 76](image)

a) SO\(_3\)-py, Et\(_3\)N, DMSO, CH\(_2\)Cl\(_2\), 0 ºC; b) NaHMDS (2 M in THF), Ph\(_3\)PCH\(_3\)Br, THF, 0 ºC, 76% (2 steps); c) CSA, CH\(_2\)Cl\(_2\):MeOH (1:1), 0 ºC, 96%.
Following the successful introduction of the vinyl group to afford alcohol 291, the next challenge was the construction of the seven-membered K-ring utilizing the previously described enone/RCM protocol (see Ch 2. § 2.3.3).

3.3 Synthesis of Enone 289

The first step in the enone/RCM strategy was the introduction of the ether side chain. Following the optimisation work undertaken during the synthesis of the IJ-model system 225, it had been found that Wittig reaction of a stabilized phosphorane with butyraldehyde allowed for the successful incorporation of the ether side chain (see Scheme 63). These conditions for the introduction of the required ether side chain were utilized in the synthesis of enone 299 (Scheme 77). Alcohol 291 was alkylated upon treatment with sodium hydride and triphenylchboroacetonylphosphorane to afford the stabilized phosphorane 298. Pleasingly, as noted in the IJ-model system 225, the Wittig reaction between butyraldehyde and phosphorane 298 furnished the desired enone 299 in 70% yield over the two steps.

```
     H   O
  291  +  (a) NaH, ClCH_2COCHPPh_3, TBAI (5 mol%), THF, rt; b) butyraldehyde, CH_2Cl_2, reflux, 70% (2 steps).
         H   O

298  +  299
```

Following isolation of the enone 299, the next step was ring closure to form the targeted seven-membered ring. Initial investigations into ring closure focussed on the use of the Grubbs second-generation catalyst 148. Unfortunately, treatment of enone 299 with ruthenium catalyst 148 resulted in no reaction (Scheme 78). As observed for the IJ-model system 225, the enone moiety appeared to render the ruthenium catalyst 148 unreactive.
The synthesis of the IJ-model system 225 utilized a three-step reduction, RCM and oxidation sequence to afford the desired bicyclic enone 228 (see Scheme 63). The same sequence was employed for the synthesis of bicyclic enone 289 (Scheme 79). Reduction of enone 299 under Luche conditions afforded alcohols 300 in good yield (1:1 mixture of diastereomers). Treatment of alcohols 300 with Hoveyda-Grubbs second-generation catalyst 150 initiated ring closure to provide alcohols 301 in 81% yield. Alcohols 301 were isolated as a separable mixture (1:1) of diastereomers. It was noted in this case, that more concentrated reaction conditions provided the best yields for the construction of the seven-membered ring. Following successful ring construction, oxidation of alcohols 301 with Dess-Martin periodinane furnished the bicyclic enone 289 in good yield.

Scheme 78

Scheme 79

a) NaBH₄, CeCl₃·7H₂O, MeOH, −78 °C, 99%, dr 1:1; b) 150 (7.5 mol%), CH₂Cl₂, reflux, 0.01 M, 81%, dr 1:1; c) DMP, CH₂Cl₂, 0 ºC, 64%.
Pleasingly, the use of the modified methodology developed during the synthesis of the IJ-model system 225 allowed the target bicyclic enone 289 to be synthesised. The next step was to investigate the installation of the required functionality for the completion of the target bicyclic ketone 226.

### 3.4 Functionalization of Enone 289

Completion of the JK-model system 226 required functionalization of the seven-membered ring in enone 289. This functionalization entailed the incorporation of an allyl side chain followed by 1,4-conjugate addition and Rubottom oxidation to install the K-ring methyl and hydroxyl substituents (Figure 21).  

![Figure 21](image)

As discussed previously (see Ch 2. § 2.4), the direct alkylation of systems similar to enone 289 is extremely difficult to perform under standard conditions. For this reason, the allyl side chain was introduced to the eight-membered ring of the IJ-model system 225 using the palladium-catalyzed Tsuji rearrangement of enol carbonate 283 (see Scheme 68). It was proposed that the required allyl side chain could be introduced to the seven-membered ring of the JK-model system 226 in a similar manner (Scheme 80). Treatment of bicyclic enone 289 with allylchloroformate and NaHMDS afforded the corresponding enol carbonate 302 in 76% yield. Upon isolation, the enol carbonate 302 was found to be unstable. After a quick purification, the enol carbonate 302 was used directly in the palladium-catalyzed rearrangement reaction. Initial attempts were made to perform the rearrangement reaction using Ph(PPh₃)₄ as the Pd⁰ source in the absence of any chiral ligand. These conditions afforded a diastereomeric mixture (1.3:1) of alkylated enones 303 favouring the desired diastereomer.
Epimerisation of the diastereomeric mixture of alkylated enones 303 with DBU improved the diastereomeric ratio from 1.3:1 to 10:1 (Scheme 81). Epimerised product 288 was confirmed to be the desired cis-diastereomer by $^1$H NMR NOE analysis (see Appendix A).

Following the isolation of alkylated enone 288, the next step to functionalize the seven-membered K-ring was the stereoselective introduction of the required methyl group. In previous studies within the group, copper-catalysed conjugate addition of dimethylzinc had been used to install a methyl group in a similar cyclic ether system (Scheme 82). In this case, the chiral phosphoramidite ligand $(S,R,R)-307$ had been employed to control the stereochemical outcome of the reaction. Unexpected direct oxidation of the intermediate zinc enolate to hydroxyketone 306 was observed and had been attributed to the action of copper salts in the presence of oxygen. 

![Scheme 80](image_url)

**Scheme 80**

a) allylchloroformate, NaHMDS (1 m in THF), THF, −78 ºC, 76%; b) Pd(PPh$_3$)$_4$ (10 mol%), THF, rt, 64%, dr 1.3:1.

![Scheme 81](image_url)

**Scheme 81**

a) DBU, PhMe, 77%, dr 10:1.
Feringa and co-workers have shown that phosphoramidites, such as $(S_{a},R,R)$-$307$ and $(R_{a},S,S)$-$308$, are excellent ligands for the asymmetric copper-catalysed conjugate addition of dialkylzinc reagents to enones (Figure 22). Excellent enantioselectivities, in both cyclic and acyclic substrates, have been achieved utilizing these chiral ligands for conjugate addition reactions.

The copper-catalysed conjugate addition of dialkylzinc reagents follows the generally accepted mechanism of cuprate reactions. A tentative general scheme can be drawn, although no intermediates have been isolated (Scheme 83). The copper(II) salt is reduced to corresponding copper(I) salt upon treatment with the dialkylzinc reagent. Reaction of the copper(I) salt with the primary organometallic reagent affords organocopper reagent A. Intermediate B arises as a result of strong coordination between the most oxophilic metal (zinc) in complex A and the oxygen atom of the enone. This complex is unable to react further and so must be transformed into the higher order cuprate C. The formation of π-complex D is the first step toward the conjugate addition. It is this step that determines the absolute configuration of the adduct. Following this π-complexation, oxidative addition affords the copper(III) intermediate E. Reductive elimination results in the formation of zinc enolate F. The copper species is then released to re-enter the catalytic cycle. Detailed investigations
revealed reductive elimination to be the rate-determining step. The nature of the substituents on the phosphorus ligand plays a key role in this step. It was noted that the higher the number of P–O bonds, the higher the rate of addition.

For the JK-model system 226, the carbon bearing the methyl group displays the opposite absolute configuration to that observed in the previously synthesised ketone 305. For this reason, it was necessary to employ the antipodal ligand \((R_a,S,S)-308\) for the copper-catalysed conjugate addition reaction. Although ligand \((R_a,S,S)-308\) is not commercially available, it was readily synthesised in moderate yield from chiral amine 309 upon treatment with phosphorus trichloride and \((R)-\text{BINOL} \) (Scheme 84).
Treatment of alkylated enone 288 with dimethylzinc and copper(II) triflate in the presence of the ligand (R<sub>a</sub>,S,S)-308 afforded ketone 287 in 30% yield (45% brsm). The low yield obtained for the reaction was attributed to the small scale (18 mg) on which the reaction was performed (Scheme 85).

Unfortunately, due to a lack of material, no useful NOE data was collected to confirm the configuration of the methyl group. The configuration was assigned based on the high stereoselectivity of the ligand (R<sub>a</sub>,S,S)-308, along with a comparison between the NMR data obtained for ketone 287 and the previously synthesised hydroxyketone 306 (Figure 23).
It was proposed that if the relationship between the H5 and H6 in ketone 287 was comparable to that between H5’ and H6’ in hydroxyketone 306, then the coupling constants of H5 in ketone 287 and H5’ in hydroxyketone 306 should be similar. It is clear, from the reported NMR data, that the splitting patterns and coupling constants of the two selected signals are similar (Table 7). This suggests that the methyl group is indeed on the same face as H5 in ketone 287.

<table>
<thead>
<tr>
<th>Hydrogen</th>
<th>Chemical shift (ppm)</th>
<th>Coupling constant (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H5’ (306)</td>
<td>3.24</td>
<td>dd, J = 9.6, 9.5</td>
</tr>
<tr>
<td>H5 (287)</td>
<td>2.83</td>
<td>dd, J = 9.4, 9.3</td>
</tr>
</tbody>
</table>

Table 7

The final step in the synthesis of the JK-model system 226 was Rubottom oxidation of ketone 287 to afford the corresponding hydroxyketone 306. It is known from previous studies, that the hydroxyl group would be introduced on the opposite face to the methyl group in the β-position. This pattern of reactivity would afford the desired JK-model system 226 (Scheme 86). Unfortunately, due to a lack of material this reaction was not investigated.

```
\begin{align*}
\text{287} & \quad \text{a-c} \quad \text{226} \\
\text{a) DIPA, } n-\text{BuLi, TESCl, Et₃N, THF, -78 °C; b) } m\text{-CPBA, NaHCO}_3, \text{PhMe, 0 °C; c) THF/H}_2\text{O/AcOH (4:2:1), rt.}
\end{align*}
```

Scheme 86
3.5 Summary

Alcohol 291 was synthesised from the commercially available tri-O-acetyl-\(\text{D-}\)glucal 208 in eight steps (Scheme 87). As in the IJ-model system 225, by employing an improved version of the initial Wittig strategy, enone 299 was obtained from alcohol 291 in two steps. Pleasingly, it was found that enone 299 could be transformed into ketone 287. Side chain introduction was accomplished by Tsuji allylation and the methyl group was installed stereoselectively upon copper-catalysed conjugate addition in the presence of the ligand \((R_a,S,S)-308\). The completion of the JK-model system 226 requires only Rubottom oxidation of ketone 287. Previous work indicates that this step should proceed smoothly to afford the desired target 226.\(^{125}\)
4.0 Two-directional approach to the IJK-ring system 224

With investigations into both model systems successfully completed, attention turned toward the development of a two-directional strategy for the synthesis of the IJK-ring system 224 of CTX3C (4) (Figure 24). Two-directional synthesis by simultaneous homologation has received significant attention over the past two decades.\textsuperscript{147} This type of strategy involves homologating both ends of the chain at the same time, followed by desymmetrization of the ends as required. When applied to appropriate target molecules, a two-directional approach offers an efficient route that requires significantly fewer steps than the corresponding linear route. The two-directional strategy designed for the synthesis of the IJK-ring system 224 featured chemistry developed during the synthesis of both model systems.

![Figure 24](image-url)
4.1 Retrosynthesis of the IJK-ring System 224

Our retrosynthetic analysis of the IJK-ring system 224 is shown below (Scheme 88). Functional group modifications followed by double retro 1,4-conjugate addition afford the alkylated tricyclic enone 310. Disconnection of both allyl side chains and subsequent alkene scission provides tetraene 312. Removal of both ether linkages affords diol 313. Using the chemistry developed during the synthesis of the two model systems, diol 313 was to be synthesised from the commercially available tri-O-acetyl-d-glucal 208.
4.2 Synthesis of Diol 313

As described previously (see Ch 2. § 2.2), alcohol 230 was prepared from the commercially available tri-O-acetyl-D-glucal 208 in eight steps. Alcohol 230 afforded easy access to triol 314; the first key target in the two-directional synthesis of the IJK-tricycle 224 (Scheme 89).

![Scheme 89]

Treatment of alcohol 230 with TBAF afforded triol 314. Purification of triol 314 proved to be difficult, but filtration through a short plug of silica gel provided material of sufficient purity. Complete TBS-protection of triol 314 proceeded smoothly to afford the alkene 315 in 88% yield over the two steps (Scheme 90).

![Scheme 90]

a) TBAF (1 M in THF), THF, 0 °C to rt; b) Imidazole, TBSCl, DMAP (25 mol%), DMF, 0 °C, 88% (2 steps).

Following the successful isolation of alkene 315, the next challenge was selective deprotection of the primary alcohol and subsequent installation of the required vinyl group (Scheme 91). Treatment of alkene 315 with camphorsulfonic acid resulted in selective deprotection of the primary alcohol to afford 316. Oxidation of alcohol 316 was performed under Parikh-Doering conditions to provide the corresponding aldehyde 317. Subsequent Wittig reaction with the ylide generated from methyltriphenylphosphonium bromide furnished diene 318 in excellent yield over the two steps.
Following the isolation of diene 318, the next step was removal of the remaining silyl ether protecting groups. Deprotection by treatment of the diene 318 with camphorsulfonic acid afforded the corresponding diol 313 in 95% yield (Scheme 92).

Following the successful introduction of the vinyl group to afford diol 313, the next challenge was to construct both the eight- and seven-membered rings simultaneously utilizing the enone/RCM protocol. It was hoped that a double enone/RCM reaction sequence would allow for the two-directional synthesis of the target tricycle 224.
4.3 Synthesis of Tricyclic Enone 311

The first step in the double enone/RCM protocol was the introduction of the two ether side chains. During the synthesis of the two model systems, various strategies were considered for the introduction of the required ether side chains. Two separate methodologies were selected for consideration in the two-directional approach to enone 311.

**tert-Butyl Ester Strategy**

The first strategy considered was to introduce the ether side chains from the corresponding tert-butyl diester 319. As detailed earlier (see Ch 2. § 2.3.3), this method was employed during the synthesis of the IJ-model system 225. Treatment of diol 313 with tert-butyl bromoacetate afforded the corresponding diester 319 in moderate yield (Scheme 93). Due to the moderate yield obtained upon extended and lengthy reaction times, no further work on this sequence was undertaken.

![Scheme 93](image)

a) tert-butyl bromoacetate, 30% aq. NaOH, TBAI (50 mol%), PhMe, rt, 5 days, 53%; b) DIBAL; c) CH₂CHMgBr.
Modification of the Initial Wittig Strategy

As seen in the synthesis of both the IJ- and JK-model systems, an improved version of the initial Wittig methodology allowed for the successful introduction of the required ether side chains (see Ch 2. § 2.3.3, § 3.3). It was believed that these reaction conditions could be employed for the two-directional synthesis of tetraene 312. First, diol 313 was alkylated upon treatment with sodium hydride and triphenylchloroacetonylphosphorane to afford phosphorane 322. Pleasingly, the Wittig reaction between butyraldehyde and the stabilized phosphonium ylide 322 afforded the desired tetraene 312 in 86% yield over the two steps (Scheme 94).

\[
\text{Scheme 94}
\]

Following the successful synthesis of the tetraene 312, the next challenge was simultaneous ring closure to form the eight-membered I-ring and seven-membered K-ring. During earlier studies performed in the group, the construction of rings in a two-directional manner via the double RCM reaction of allylic ethers, enol ethers or alkynyl ethers had been explored (see Ch 1. § 2.4.). With these results in mind, ring closure to form the required tricyclic carbon skeleton of the IJK-ring system 224 was investigated. Treatment of tetraene 312 with either Grubbs first or second generation catalyst 61 or 148, resulted in the recovery of starting material without formation of the required
product (Scheme 95). This result was not unexpected because in both model systems neither the eight- nor seven-membered ring was closed upon treatment of the corresponding enone with these ruthenium catalysts. The lack of reactivity toward ring closure was attributed to unproductive complexation between the substrate and the catalyst (see Ch 2. § 2.3.2).

During the synthesis of the two model systems it had been shown that RCM of the corresponding allylic alcohol precursors 273 and 300 resulted in successful ring construction. A three-step reduction, RCM and oxidation sequence was employed for the construction of both the eight-membered L-ring and the seven-membered K-ring (Scheme 96). It was believed that this three-step sequence could be employed for the two-directional synthesis of the tricyclic enone 311. The first step in the sequence was Luche reduction of both enones in the tetraene 312 to give the corresponding diol 323. Diol 323 was isolated in excellent yield as a statistical mixture of diastereomers.

Scheme 95

a) 61 or 148 (20 mol%), CH₂Cl₂, reflux.
Following the synthesis of diol 323, the next step in the sequence was double RCM reaction to afford the desired tricyclic ether 324. This step necessitated some optimisation of the reaction conditions. During the model syntheses, it was discovered that reaction concentration had a significant effect on the yield of the RCM reaction. The optimum reaction conditions for the construction of the eight- and seven-membered rings, differ in terms of both reaction concentration and catalyst loading (Table 8). In the case of the eight-membered ring, low concentration (0.001 M) and a catalyst loading of 5 mol% afforded the desired alcohol 268 in 96% yield. For the construction of the seven-membered ring, the best yields were observed at a higher concentration (0.01 M) and a slightly higher catalyst loading of 7.5 mol%.

Scheme 96

a) NaBH₄, CeCl₃·7H₂O, MeOH, −78 °C, 96%, dr 1:1:1:1; b) RCM.
Table 8

These results suggested that some optimisation of both the reaction concentration and catalyst loading would be required to obtain a high yield from the double RCM reaction. Initial studies revealed a catalyst loading of 20 mol% afforded the highest conversion of starting material. This requirement for a higher catalyst loading was not unexpected because the double RCM reaction constructs two rings simultaneously. With regard to reaction concentration, complete conversion of starting material was only observed for the two higher concentrations investigated, 0.01 M and 0.005 M. Unfortunately, purification of diol 324 proved to be problematic due to decomposition on silica. For this reason, the conversion was noted and the crude reaction mixture was then taken directly on to the next step (Scheme 97). Oxidation of diol 324 with Dess-Martin periodinane afforded tricyclic ether 311 in 39% yield over the two steps. It is believed, that with further investigation, the reaction conditions could be optimised further and yields comparable to those achieved for the corresponding steps in the two model syntheses could be obtained.
With the core of the polycyclic carbon skeleton now in place, the remaining challenge was efficient functionalization of the eight- and seven-membered rings to afford the IJK-ring system 224. Functionalization entailed the incorporation of an allyl side chain by alkylation and introduction of a methyl substituent by conjugate addition to each ring, followed by Rubottom oxidation on the seven-membered ring. (Figure 25).

The first step in the sequence used to functionalize the IJK-ring system 224 was the simultaneous incorporation of the two allyl side chains. Ether 311 was first treated with allylchloroformate and sodium bis(trimethylsilyl)amide solution to afford carbonate 325 in good yield (Scheme 98).
a) allylchloroformate, NaHMDS (1 M in THF), THF, −78 ºC, 69%.

Scheme 98

It was proposed that palladium-catalysed rearrangement of 325 would afford the desired alkylated tricyclic ether 310. During the synthesis of both model systems palladium-catalysed rearrangement had been employed to introduce the requisite allyl side chain (see Ch 2. § 2.4, § 3.4). In the case of the eight-membered I-ring, it was found that performing the rearrangement in the presence of the (S)-tBu-PHOX ligand (S)-282 afforded the desired alkylated enone 227 with a diastereomeric ratio of >20:1 (Scheme 99).

a) Pd(PPh₃)₄ (10 mol%), (S)-tBu-PHOX (S)-282 (25 mol%), THF, rt, 85%, dr >20:1.

Scheme 99

The highlighted stereocentre (*) in the IJ-model system 227 has S-configuration (Figure 26). The desired configuration was installed through the use of the chiral (S)-tBu-PHOX ligand (S)-282 in the palladium-catalyzed rearrangement. The corresponding highlighted stereocentre (*) in the JK-model system 226 has R-configuration.
Ideally, the palladium-catalyzed rearrangement reaction used to install the allyl side chain in the JK-model system 226 would have been performed using the \((R)-tBu-PHOX\) ligand \((R)-282\). Unfortunately the \((R)-tBu-PHOX\) ligand \((R)-282\) is not commercially available and, unlike the \((S)-tBu-PHOX\) ligand \((S)-282\), cannot be synthesised readily from straightforward starting materials.\(^{148}\) An alternative option would have been to utilize the commercially available \((R)-iPr-PHOX\) ligand 326 (Figure 27).

The use of the \((R)-iPr-PHOX\) ligand 326 was discounted because the two-directional approach to the IJK-ring system 224 requires the simultaneous alkylation of both the eight- and seven-membered rings. Consequently, it was only possible to employ one chiral ligand in the palladium-catalysed rearrangement of carbonate 325. The \((S)-tBu-PHOX\) ligand \((S)-282\) was selected for use in the rearrangement because the epimerisation at the stereocentre bearing the allyl side chain in the seven-membered ring (dr 1.3:1 to 10:1) was far more successful than epimerisation at the corresponding stereocentre in eight-membered ring (dr 1.8:1 to 5:1). The palladium-catalysed rearrangement of bicyclic carbonate 302 in the presence of the \((S)-tBu-PHOX\) ligand \((S)-282\) was investigated (Scheme 100). Treatment of carbonate 302 with \(\text{Pd(PPh}_3\text{)}_4\) and \((S)-tBu-PHOX\) ligand \((S)-282\) afforded alkylated enone 327 as a 1:14 mixture of diastereomers, favouring the undesired diastereomer. Epimerisation of 327 with DBU afforded the desired \(cis\)-product 288 in 83% yield with a diastereomeric ratio of 10:1.
Following successful epimerisation of the alkylated enone 327, it was decided to perform the double palladium-catalysed rearrangement of carbonate 325 in the presence of the (S)-tBu-PHOX ligand (S)-282. It was expected that this reaction would allow the allyl side chain on the eight-membered ring to be installed with the correct stereochemistry at the newly created stereocentre and that subsequent epimerisation with DBU should correct the stereochemistry at the stereocentre bearing the allyl side chain in the seven-membered ring. The palladium-catalysed rearrangement of carbonate 325 afforded alkylated tricyclic ethers 328 in good yield as a complex mixture of diastereomers (Scheme 101). Epimerisation of 328 using DBU afforded the target tricyclic ether 310. The disappointingly low yield obtained for the epimerisation reaction was likely due to a combination of two factors: decomposition of the starting material and the small scale on which the reaction was performed.
The next stage in the functionalization of the tricyclic ring system 310 was introduction of the methyl substituents by ‘double’ 1,4-conjugate addition. Again, data obtained from the model studies allowed suitable reaction conditions to be identified for the two-directional approach. In an effort to discover conditions that would allow for the stereoselective ‘double’ 1,4-conjugate addition on both rings, the two sets of reaction conditions developed in the model studies were applied to both the eight- and seven-membered rings. Table 9 details the 1,4-conjugate addition reaction conditions developed for the synthesis of the JK-model system 226. These conditions were found to introduce the methyl group on the seven-membered K-ring with the desired stereochemical outcome and with good selectivity. However, when these conditions were applied to the eight-membered enone 227, ketones 329 were isolated as a 1:1 mixture of diastereomers. Consequently, due to the lack of selectivity observed in the case of addition to eight-membered cyclic enone, these reaction conditions proved unsuitable for use in the two-directional strategy.
<table>
<thead>
<tr>
<th>Starting material</th>
<th>Reaction conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="288" /></td>
<td>Me$_2$Zn, CuOTf$_2$ (6 mol%), (R$_a$,S,S)-308 (12 mol%), PhMe.</td>
<td><img src="image" alt="287" /></td>
</tr>
<tr>
<td><img src="image" alt="227" /></td>
<td>Me$_2$Zn, CuOTf$_2$ (6 mol%), (R$_a$,S,S)-308 (12 mol%), PhMe.</td>
<td><img src="image" alt="329" /></td>
</tr>
</tbody>
</table>

30% yield (45% brsm)

53% yield (dr 1:1)

**Table 9**

**Table 10** details the 1,4-conjugate addition reaction conditions developed during the synthesis of the IJ-model system 225. Under these conditions, the methyl group could be installed on the eight-membered I-ring with the desired stereochemical outcome in a highly stereoselective manner. When these conditions were applied to conjugate addition to the seven-membered enone 288, ketone 287 was isolated in low yield. Pleasingly, the reaction conditions appear to allow for the simultaneous stereoselective introduction of the methyl group to both rings. The disappointing yield observed for the reaction, was attributed to the low conversion of the starting material. It is believed that with further studies this poor conversion could be improved.
Based on the results noted in Tables 9 and 10, it appears that the use of a higher order cuprate reagent, Me$_2$Cu(CN)Li$_2$, should allow stereoselective introduction of the required methyl groups to both the eight- and seven-membered rings. The stereoselectivity of the 1,4-conjugate addition reaction was attributed to substrate control. Unfortunately, due to a lack of material and time this reaction could not be investigated on the alkylated tricyclic ether 310 (Scheme 102).

Scheme 102
4.5 Summary

Alcohol 230 was synthesised from the commercially available tri-O-acetyl-d-glucal 208 in eight steps. Utilizing chemistry developed during the synthesis of the JK-model system, alcohol 230 was converted into the diol 313 in six steps. Diol 313 proved to be a key target in the synthesis of the IJK-tricyclic system 224. From diol 313, alkylated tricyclic ether 310 was synthesised via a two-directional strategy based on the chemistry developed during the two model syntheses. Conditions that allow the simultaneous 1,4-conjugate addition to both the eight- and seven-membered rings have been identified by performing studies on the corresponding model systems (Scheme 103).

Completion of the IJK-ring system 224 from the alkylated tricyclic ether 330 requires some further functionalization. Rubottom oxidation of the seven-membered ring is the final step required to afford the desired target 224. Unfortunately, this reaction is unlikely to be fully chemoselective and affect only the seven-membered ring. For this reason, reduction of the eight-membered ring ketone and subsequent protection is likely to be required before the Rubottom oxidation (Scheme 104). Depending on the differing reactivities of the two ketones, it is possible that reduction and protection of the seven-membered ring ketone will be required.
5.0 Alternative Two-directional Strategy

While working toward the synthesis of the IJK-ring system 224 (see Ch 2. § 4.0), an alternative two-directional approach that employed a completely symmetrical strategy was also investigated. This novel strategy would rely on the late-stage desymmetrisation of the meso tricyclic intermediate 332 (Scheme 105).
5.1 Alternative Retrosynthetic Analysis of the IJK-ring System 224

Our retrosynthetic analysis of the IJK-ring system 224 following the alternative two-directional strategy is shown below (Scheme 106). Functional group modifications followed by double retrosynthetic 1,4-conjugate addition afford the tricyclic bis-enone 310. Retrosynthetic ring contraction of the eight-membered ring affords the key meso tricyclic bis-enone 332. Disconnection of both allyl side chains, followed by a retrosynthetic RORCM reaction provides bicycle 333. Removal of both ether linkages affords diol 334 and further functional group modifications provide the known oxabicyclic ketone 335. Retro [4+3] cycloaddition delivers furan and tetrabromoacetone.

Scheme 106
5.2 Synthesis of Oxabicycle 335

The [4+3] cycloaddition reaction of allylic cations and dienes provides a convenient route to bicyclo[3.2.1]ketones such as oxabicycle 335. Oxabicycle 335 has been known in the literature for over four decades.\(^{149}\) It has proven to be a useful and highly versatile building block in organic synthesis. Recent applications include the synthesis of various tetrahydropyran units that appear in marine natural products, pseudo-C-glycosides and other bioactive substances e.g. bryostatin 1 (336) and (+)-mevinolin (153) (Scheme 107).\(^{150}\)

![Scheme 107](image)

Bicyclic ketone 335 was originally prepared by the reaction of 2-methoxyallyl bromide with silver trifluoroacetate in the presence of furan.\(^{151}\) More recently, Hoffmann and co-workers have reported an inexpensive and scalable synthesis of oxabicycle 335 from furan and tetrabromoacetone.\(^{152}\) Our synthesis began with the preparation of tetrabromoacetone (Scheme 108). Acetone was treated with bromine and an aqueous solution of hydrogen bromide to afford tetrabromoacetone in moderate yield. The next step was the [4+3] cycloaddition reaction with furan. The cycloaddition reaction was performed in the presence of activated zinc and triethyl borate to afford a mixture of brominated adducts 337 and 338. It was noted, that the addition of a catalytic amount of bromine was required for the initiation of the cycloaddition reaction. Debromination of cycloadducts 337 and 338 was achieved using a suspension of zinc-copper couple and ammonium chloride in methanol to afford the target bicycle 335 in 45% yield over the two steps.
It is known that 335 is prone to decomposition under acidic conditions.\textsuperscript{152} In an attempt to avoid decomposition, the bicyclic ketone 335 was filtered through a short plug of potassium carbonate to ensure the removal of any remaining traces of hydrogen bromide. Hoffmann has proposed that the cycloaddition reaction can be visualized as a single electron transfer (SET) process (Scheme 109).
SET and Lewis acid mediated ionic steps, facilitated by triethyl borate, generate the crucial boron oxyallyl cation $341/342$. The cation is then captured by furan to afford the corresponding brominated bicyclic ether $337/338$. High temperature reduction then delivers the target bicycle $335$. Following the synthesis of $335$, the next challenge was functionalization of the scaffold to afford diol $334$.

5.3 Towards the Synthesis of Diol $334$

Efforts to synthesise the diol $334$ began by once more following procedures detailed by Hoffmann and co-workers.\textsuperscript{152} Oxabicycle $335$ was deprotonated with lithium diisopropylamine, and the resulting enolate trapped with triethylsilyl chloride to afford silyl enol ether $343$ (Scheme 110). Oxidation with $m$-CPBA effected Rubottom oxidation to provide $\alpha$-hydroxyketone $344$. PMB-protection of hydroxyketone $344$ afforded ketone $345$ in 84% yield. Due to the base sensitivity of hydroxyketone $344$, the protection reaction was performed under acid catalysis using 4-methoxybenzylicloroacetamidate and a catalytic amount of camphorsulfonic acid.

\[
\begin{align*}
\text{Scheme 110} \\
\text{a)} & \quad \text{LDA, THF, } -78 \, ^\circ\text{C, then } 335, \text{TESCl, Et}_3\text{N, THF, } -78 \, ^\circ\text{C;} \\
\text{b)} & \quad m\text{-CPBA, THF/H}_2\text{O (1:1), } 0 \, ^\circ\text{C, then TFA, } 0 \, ^\circ\text{C, } 36\% \ (2 \text{ steps}); \\
\text{c)} & \quad 4\text{-methoxybenzylicloroacetamidate, CSA (10 mol%), CH}_2\text{Cl}_2, 0 \, ^\circ\text{C to rt, } 84\%.
\end{align*}
\]

Unfortunately, the yield obtained for the formation of hydroxyketone $344$ was disappointingly low. The problem appeared to arise from the incomplete conversion of the silyl enol ether $343$ into the hydroxyketone $344$ and because the enol ether $343$ was unstable to purification on silica gel, a significant
amount of material was lost due to decomposition on the column. All attempts to improve the yield obtained for this sequence were unsuccessful.

The reaction sequence was then repeated to afford ketone 348 (Scheme 111). Ketone 345 was deprotonated with lithium diisopropylamine and the resulting enolate trapped with triethylsilyl chloride to afford silyl enol ether 346. Oxidation with dimethyl dioxirane furnished the rearranged Rubottom product, which was desilylated in situ to provide α-hydroxyketone 347. PMB-protection of hydroxyketone 347 afforded ketone 348 in 63% yield.

Scheme 111

Unfortunately, the yield from the Rubottom oxidation reaction was only slightly improved upon the replacement of m-CPBA with dimethyl dioxirane. As before, incomplete conversion of the silyl enol ether 346 into the hydroxyketone 348 led to a significant loss of material during purification. The low-yielding Rubottom oxidation steps made it very difficult to bring significant quantities of material through this sequence. Consequently, it was decided that no further work would be undertaken on this route and efforts would be focused on the initial two-directional strategy.
5.4 Summary

The oxabicyclic ketone 335 was synthesised from acetone in three steps. Functionalization to afford ketone 348 using sequential Rubottom oxidation reactions was completed in six steps. Unfortunately, due to the poor yields observed during the sequence no further investigation into this route was undertaken (Scheme 112).

The next step in the alternative two-directional approach would have been deoxgenation of ketone 348 followed by the subsequent deprotection of the resulting bicyclic ether to afford diol 334 (Scheme 113). The metathesis precursor 333 would be obtained utilizing the enone formation protocol detailed earlier (see Ch 2. § 2.3). RORCM reaction of 333 should afford the tricyclic ether 349. There is literature precedent for the use of a similar RORCM process to construct a tricyclic system.\textsuperscript{153} Alkylation of tricycle 349, upon palladium-catalysed rearrangement of the corresponding enol carbonate, should afford the meso-intermediate 332.
The next challenge would be desymmetrisation and ring expansion to form the eight-membered carbon skeleton of the I-ring (Scheme 114). For this approach to be successful, it would be necessary to identify conditions for the selective reduction of one of the carbonyl groups. The resulting alcohol would be protected as the corresponding TBS ether and subsequent 1,4-conjugate reduction of enone 350 with enolate trapping should deliver silyl enol ether 351.\textsuperscript{154} Cyclopropane 352 could be obtained via the regio- and stereoselective cyclopropanation of the electron-rich silyl enol ether 351.\textsuperscript{155} Treatment of cyclopropane 352 with iron(III) chloride and triethylamine should deliver the desired ring-expanded enone. Removal of the TBS ether and subsequent oxidation would then deliver the tricyclic ether 310. At this point, the route intersects with the initial two-directional strategy.

\begin{center}
\textbf{Scheme 114}
\end{center}
6.0 Conclusions

In order to investigate the chemistry required for the synthesis of the IJK-ring system 224 two separate model systems were designed and investigated. The IJ-model 225 was constructed in sixteen steps from tri-O-acetyl-d-glucal 208 (Scheme 115). Completion of the model system allowed the construction and functionalization of the eight-membered I-ring to be explored. The ketone 287 was obtained in seventeen steps from tri-O-acetyl-d-glucal 208. Rubottom oxidation of ketone 287 should afford the targeted JK-model system 226. Precedent shows that the Rubottom oxidation should proceed with the desired stereochemistry.125

Both model systems employed a two-stage enone formation/RCM protocol for ring construction. After some optimisation, suitable RCM precursors for both model systems were synthesised (Figure 28). It was noted that by using an allylic alcohol as the RCM precursor, instead of the corresponding enone, the yields for ring construction by RCM were markedly improved.
Finally, after studies towards the model systems were complete, a two-directional strategy towards the IJK-ring system 224 was considered (Scheme 116). The initial two-directional approach built upon the chemistry developed during the synthesis of the two model systems. Pleasingly, a suitable route that allowed for the successful isolation of alkylated tricyclic ether 310 was developed. The two-directional nature of the strategy was observed in the conversion of diol 313 to tricyclic ether 310.

An alternative two-directional strategy, employing late stage desymmetrisation of meso-intermediate 332, was also considered. Unfortunately, due to the low yields encountered in the initial stages of the sequence, further optimisation will be required before this strategy can be considered to be synthetically viable (Scheme 117).
Chapter 3: Experimental
Chapter 3: Experimental Section

Apparatus

$^1$H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at ambient temperature. The spectra are reported as follows: chemical shift in ppm relative to CDCl$_3$ ($\delta = 7.26$), integration, multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (br), apparent (app) or a combination of these], coupling constant(s) $J$ (Hz) and assignment.$^{13}$C NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at 101 MHz and 126 MHz at ambient temperature. The spectra are reported as follows: chemical shift in ppm relative to the central resonance of CDCl$_3$ ($\delta = 77.16$) and assignment. DEPT 135 and two-dimensional NMR spectroscopy (COSY, HSQC) were used, where appropriate, to assist with the assignment of signals in the $^1$H and $^{13}$C NMR spectra. IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The IR spectrum of the compound (solid or liquid) was detected directly as a thin layer, without any sample preparation, at ambient temperature. High resolution mass spectra (HRMS) were obtained under EI, CI and ESI conditions by the analytical services of the University of Glasgow. Melting points were recorded with an Electrothermal IA 9100 apparatus. Specific rotations ($[\alpha]_D$) were measured on an Autopol V Automatic polarimeter.

Chromatography

Column chromatography was performed under pressure using silica gel (Flurochem LC60A, 35–70 micron, 60A) as solid support and HPLC grade solvent as eluent. Petroleum ether (40–60 ºC) was used for column chromatography. Reactions were monitored by thin layer chromatography using Merck $F_{254}$ silica gel covered aluminium plates. Thin layer chromatography plates were viewed under UV-light and/or developed using either a potassium permanganate solution (3 g of KMnO$_4$, 20 g of K$_2$CO$_3$, 5 mL 5% NaOH aq. and 300 mL H$_2$O) or an acidic ethanolic anisaldehyde solution (15 g anisaldehyde, 250 mL ethanol, 2.5 mL conc. H$_2$SO$_4$).
Nomenclature

The numbering which appears on the structures corresponds to the assignments of NMR spectra.

Reagents

Liquid reagents were distilled prior to use if necessary. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

General reaction conditions

Air and/or moisture sensitive reactions were performed in glassware that was flame dried prior to use, under an atmosphere of argon. Organic solvents were dried using a Pure Solv™ purification system.
[(2R,3S)-3-Acetoxy-6-methoxy-3,6-dihydro-2H-pyran-2-yl]methylaceta
te (232)

\[
\begin{array}{c}
\text{MeO} \quad \text{O} \\
\text{H} \\
\text{O} \\
\text{O} \quad \text{O}
\end{array}
\]

\[C_{11}H_{18}O_6 \]

Molecular weight: 244.24 g.mol\(^{-1}\)

Boron trifluoride diethyl etherate (5.00 mL, 40.4 mmol) and anhydrous MeOH (4.10 mL, 101 mmol) were added to a solution of 208 (25.0 g, 91.8 mmol) in anhydrous CH\(_2\)Cl\(_2\) (120 mL). The reaction mixture was stirred for 3 h at rt, then the reaction was quenched with a saturated aqueous solution of NaHCO\(_3\) (175 mL). The solution was diluted with H\(_2\)O:CH\(_2\)Cl\(_2\) (1:1, 400 mL). The phases were separated and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. The residual crude product was filtered through a short pad of silica gel (petroleum ether–Et\(_2\)O, 1:1) to afford 232 (18.4 g) as a pale yellow oil that was used without further purification.
A solution of crude acetal 232 [56.3 mmol] in anhydrous dioxane (100 mL) was added dropwise to a suspension of lithium aluminium hydride (4.27 g, 113 mmol) in anhydrous dioxane (300 ml) at reflux. The reaction mixture was stirred for 1 h at reflux, then cooled to rt and diluted with Et₂O (175 mL). The solution was cooled to 0 °C, then the reaction was quenched by the addition of H₂O (10 mL), 6 M NaOH (10 mL) and H₂O (20 mL). The reaction mixture was warmed to rt and MgSO₄ (ca 15 g) was added. After 45 min, the solution was filtered through a pad of Celite and the pad washed with Et₂O (4 x 150 mL). The resulting filtrate was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 3:5) to afford diol 233 (5.96 g, 81% yield over two steps) as a colourless oil.

Rᵥ = 0.48 (EtOAc);
[a]₀ (26.7 ºC, CHCl₃) = +89.9 (c = 1.05);
{Lit.¹⁵⁷ [a]₀ (26 ºC, CHCl₃) = +80.4 (c = 1.10)};
IR: ν max 3351, 2924, 1652, 1444, 1234, 1133, 1063 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δH 6.32 (1H, ddd, J = 5.9, 1.9, 1.9 Hz, CH-C1), 4.67 (1H, ddd, J = 5.9, 5.2, 2.6 Hz, CH-C2), 3.98 (1H, dddd, J = 8.6, 8.6, 5.6, 5.6 Hz, CH-C4), 3.94–3.84 (2H, m, CH₂-C6), 3.67 (1H, ddd, J = 8.6, 4.1, 4.1 Hz, CH-C5), 2.83 (1H, d, J = 5.6 Hz, OH), 2.47 (1H, dd, J = 7.0, 5.7 Hz, OH), 2.38–2.29 (1H, m, CH₂-C3), 2.06 (1H, dddd, J = 16.5, 8.6, 2.6, 2.6 Hz, CH₂-C3);
¹³C NMR: (126 MHz, CDCl₃) δC 142.9 (CH-C1), 98.5 (CH-C2), 78.7 (CH-C5), 64.6 (CH-C4), 62.4 (CH₂-C6), 29.3 (CH₂-C3);
HRMS: (EI⁺) for C₆H₁₀O₃ ([M⁺]) calculated 130.0630, found 130.0627, Δ -2.5 ppm.
(4aR,8aR)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxine (241)

Pyridinium p-toluenesulfonate (116 mg, 0.460 mmol) was added to an ice-cooled solution of 233 (300 mg, 2.31 mmol) and p-anisaldehyde dimethylacetal (0.60 mL, 3.5 mmol) in anhydrous acetonitrile (5 mL). The reaction mixture was stirred for 30 min at 0 °C, then warmed to rt and stirred overnight. The solution was diluted with CH₂Cl₂ (10 mL) and washed with a saturated aqueous solution of NH₄Cl (10 mL). The two phases were separated and the organic phase was dried (MgSO₄) then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 98:2) afforded enol ether 241 (339 mg, 59% yield) as a colourless solid.

\[ R_f = 0.72 \text{ (petroleum ether–Et}_2\text{O, 1:1);} \]
\[ [\alpha]_D^{24.7 \degree \text{C, CHCl}_3} = +56.6 \ (c = 1.16); \]
\[ \{\text{Lit.}^{118a} [\alpha]_D^{25 \degree \text{C, CH}_2\text{Cl}_2} = +40.9 \ (c = 0.2)\}; \]
\[ \text{m.p.} = 104–106 \degree \text{C}; \]
\[ \text{IR: } \nu_{\text{max}} 2980, 2872, 1641, 1614, 1587, 1518, 1372, 1247, 1174, 1034, 1014 \text{ cm}^{-1}; \]
\[ ^1\text{H NMR: } (500 \text{ MHz, CDCl}_3) \delta_H 7.46–7.41 \ (2\text{H, m, CH–C}10), 6.92–6.88 \ (2\text{H, m, CH–C9}), 6.33 \ (1\text{H, ddd, } J = 5.8, 2.2, 1.6 \text{ Hz, CH–C1}), 5.59 \ (1\text{H, s, CH–C7}), 4.74 \ (1\text{H, ddd, } J = 5.8, 5.8, 2.2 \text{ Hz, CH–C2}), 4.42–4.34 \ (1\text{H, m, CH–C5}), 3.96–3.89 \ (1\text{H, m, CH–C4}), 3.82–3.76 \ (5\text{H, m, CH}_3\text{–C12 and CH}_2\text{–C6}), 2.35 \ (1\text{H, dddd, } J = 16.2, 5.8, 5.8, 1.9 \text{ Hz CH}_2\text{–C3}), 2.25 \ (1\text{H, dddd, } J = 16.2, 9.7, 2.2, 2.2 \text{ Hz, CH}_2\text{–C3}); \]
\[ ^{13}\text{C NMR: } (126 \text{ MHz, CDCl}_3) \delta_C 160.3 \ (C–C11), 143.2 \ (CH–C1), 130.1 \ (C–C8), 127.6 \ (2 \times CH–C10), 113.9 \ (2 \times CH–C9), 101.8 \ (CH–C7), 98.8 \ (CH–C2), 75.2 \ (CH–C4), 70.1 \ (CH–C5), 69.0 \ (CH_2–C6), 55.5 \ (CH_3–C12), 26.5 \ (CH_2–C3); \]
\[ \text{HRMS: (EI') for C}_{14}\text{H}_{16}\text{O}_4 ([M]^+) \text{ calculated 248.1049, found 248.1046, } \Delta -1.2 \text{ ppm.} \]
Camphorsulfonic acid (23.3 mg, 0.100 mmol) was added to a solution of 233 (250 mg, 1.92 mmol) and benzaldehyde dimethylacetal (0.15 mL, 1.0 mmol) in anhydrous DMF (5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The solution was neutralised with solid NaHCO₃ (until gas evolution ceased), diluted with EtOAc (15 mL) and washed with brine (15 mL). The two phases were separated and the organic phase was dried (MgSO₄) then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 19:1) afforded 240 (224 mg, 54% yield) as a colourless solid.

Rᵋ = 0.80 (petroleum ether—Et₂O, 1:1);
[α]D (25.4 °C, CHCl₃) = +29.6 (c = 0.93);
m.p. = 107—109 °C;
IR: νmax 3063, 2986, 2876, 1640, 1380, 1236, 1130, 1084, 1072, 1003 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δH 7.54—7.49 (2H, m, CH–Ar), 7.42—7.34 (3H, m, CH-Ar), 6.34 (1H, d, J = 5.9 Hz, CH–C1), 5.63 (1H, s, CH–C7), 4.75 (1H, ddd, J = 5.9, 5.9, 2.2 Hz, CH–C2), 4.45—4.36 (1H, m, CH–C5), 3.95 (1H, dddd, J = 15.8, 7.3, 1.6, 1.6 Hz, CH–C4), 3.85—3.75 (2H, m, CH₂-C6), 2.41—2.32 (1H, m, CH₂-C3), 2.32—2.22 (1H, m, CH₂-C3);
¹³C NMR: (126 MHz, CDCl₃) δC 143.2 (CH–C1), 137.6 (C–Ar), 129.2 (2 x CH–Ar), 128.5 (2 x CH–Ar), 126.3 (CH–Ar), 101.9 (CH–C7), 98.8 (CH–C2), 75.2 (CH–C4), 70.1 (CH–C5), 69.1 (CH₂-C6), 26.5 (CH₂-C3);
HRMS: (EI⁺) for C₁₃H₁₄O₃ ([M⁺]⁺) calculated 218.0943, found 218.0947, Δ +2.1 ppm.
**tert-Butyl[(2R,3S)-3-[(tert-butyldimethylsilyl)oxy]-3,4-dihydro-2H-pyran-2-yl]methoxy]dimethylsilane (234)**

\[
\begin{align*}
\text{H} & \quad \text{OTBS} \\
1 & \quad 2 \\
\text{O} & \quad 3 \\
\text{H} & \quad \text{OTBS}
\end{align*}
\]

\[\text{C}_{18}\text{H}_{38}\text{O}_{3}\text{Si}_{2}\]

**Molecular weight:** 358.66 g mol\(^{-1}\)

TBSCl (1.84 g, 12.2 mmol) and imidazole (1.30 g, 19.0 mmol) were added to a solution of 233 (500 mg, 3.80 mmol) in anhydrous DMF (15 mL) at 0 °C. The reaction mixture was warmed to rt, stirred overnight then diluted with Et\(_2\)O (30 mL). The organic phase was washed with H\(_2\)O (5 x 50 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et\(_2\)O, 99:1) afforded enol ether 234 (1.09 g, 80% yield) as a colourless oil.

| Rf | 0.73 (petroleum ether–Et\(_2\)O, 1:1); |
| d\(_{\alpha}\) | (26.1 °C, CHCl\(_3\)) = +76.3 (c = 1.09); |
| Lit.\(^{116}\) | [d\(_{\alpha}\)] \(22.6 \text{ °C}, \text{CHCl}_3\) = +75.3 (c = 1.02); |

**IR:** \(\nu_{\text{max}}\) 2955, 2929, 2858, 1657, 1473, 1254, 1240, 1106, 1089, 1051 cm\(^{-1}\);

**\(^1\)H NMR:** (500 MHz, CDCl\(_3\)) \(\delta\) 6.32 (1H, d, \(J = 5.8 \text{ Hz}, \text{CH-C1}\)), 4.57 (1H, ddd, \(J = 5.8, 5.8, 2.4 \text{ Hz}, \text{CH-C2}\)), 3.94–3.88 (2H, m, CH-C4 and CH\(_2\)-C6), 3.84 (1H, dd, \(J = 11.3, 4.8 \text{ Hz}, \text{CH}_2\)-C6), 3.56 (1H, ddd, \(J = 8.6, 4.8, 2.4 \text{ Hz}, \text{CH-C5}\)), 2.26–2.20 (1H, m, CH\(_2\)-C3), 2.03 (1H, ddd, \(J = 16.4, 8.8, 2.4, 2.4 \text{ Hz}, \text{CH}_2\)-C3), 0.90 (9H, s, \text{CH}_3-tBu), 0.89 (9H, s, \text{CH}_3-tBu), 0.09 (3H, s, \text{CH}_3-Me), 0.08 (3H, s, \text{CH}_3-Me), 0.07 (6H, s, \text{CH}_3-Me);

**\(^13\)C NMR:** (126 MHz, CDCl\(_3\)) \(\delta\) 143.4 (CH-C1), 97.6 (CH-C2), 80.0 (CH-C5), 64.4 (CH-C4), 62.7 (CH\(_2\)-C6), 30.6 (CH\(_2\)-C3), 26.2 (CH\(_3\)-tBu), 25.9 (CH\(_3\)-tBu), 18.7 (C-tBu), 18.1 (C-tBu), −4.1 (CH\(_3\)-Me), −4.8 (CH\(_3\)-Me), −4.9 (CH\(_3\)-Me), −5.1 (CH\(_3\)-Me);

**HRMS:** (ESI) for C\(_{19}\)H\(_{38}\)Na\(_3\)O\(_3\)Si\(_2\) ([M+Na]\(^{+}\)) calculated 381.2257, found 381.2252, \(\Delta +2.8 \text{ ppm}\).
**tert-Butyl[[(3R,4S)-4-[(tert-butyldimethylsilyl)oxy]-2,7-dioxabicyclo[4.1.0]heptan-3-yl]methoxy]dimethylsilane (235)**

A freshly distilled solution of dimethyl dioxirane (28.0 mL of a 0.09 M solution in acetone, 2.42 mmol) was added to a solution of 234 (668 mg, 1.86 mmol) in CH₂Cl₂ (25 mL) at −78 ºC. The reaction mixture was stirred for 30 min at −78 ºC. The organic phase was then washed with a saturated aqueous solution of NaHCO₃ (75 mL), dried (MgSO₄) and concentrated under reduced pressure at 4 ºC to afford a diastereomeric mixture of epoxides 235 (687 mg, dr 4:1) as a colourless oil. Epoxides 235 were then used directly without further purification.

**Allylmagnesium bromide**


Allylmagnesium bromide (5.31 mL of a 0.7 M solution in Et₂O, 3.72 mmol) was added to a solution of crude epoxide 235 [1.86 mmol] in anhydrous THF (35 mL) at 0 ºC. The reaction mixture was stirred for 2 h at 0 ºC, then the reaction was quenched with a saturated aqueous solution of NH₄Cl (40 mL). The two phases were separated and the aqueous phase extracted with Et₂O (3 x 40 mL). The organic extracts were combined, washed with brine (75 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 19:1) afforded alcohol 236 (488 mg, 64% yield, dr > 20:1) as a colourless solid.
$R_f = 0.39$ (petroleum ether–Et$_2$O, 1:1);

$[\alpha]_D$ (24.4 °C, CHCl$_3$) = +18.7 (c = 0.95);

m.p. = 41–43 °C;

IR: $\nu_{\text{max}}$ 3307, 2929, 2856, 1473, 1462, 1250, 1165, 1142, 1096, 1032, 1018 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$H 5.88 (1H, dddd, $J = 17.1$, 10.2, 7.4, 7.4 Hz, CH–C8), 5.20–5.16 (1H, m, CH$_2$–C9), 5.16–5.10 (1H, m, CH$_2$–C9), 3.84–3.77 (2H, m, CH–C4 and CH$_2$–C6), 3.72 (1H, dd, $J = 11.0$, 4.8 Hz, CH$_2$–C6), 3.58 (1H, dd, $J = 11.1$, 1.7 Hz, CH–C2), 3.30–3.22 (2H, m, CH–C1 and CH–C5), 2.56 (1H, s, OH), 2.29 (2H, d, $J = 7.4$ Hz, CH$_2$–C7), 2.01 (1H, ddd, $J = 12.7$, 4.3, 1.7 Hz, CH$_2$–C3), 1.57 (1H, dd, $J = 12.7$, 8.7 Hz, CH$_2$–C3), 0.89 (9H, s, CH$_3$–tBu), 0.88 (9H, s, CH$_3$–tBu), 0.07 (6H, s, CH$_3$–Me), 0.06 (3H, s, CH$_3$–Me), 0.05 (3H, s, CH$_3$–Me);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$C 133.0 (CH–C8), 119.3 (CH$_2$–C9), 81.8 (CH–C5), 73.6 (CH–C1), 69.9 (CH–C2), 65.4 (CH–C4), 62.5 (CH$_2$–C6), 42.2 (CH$_2$–C7), 42.1 (CH$_2$–C3), 26.1 (3 x CH$_3$–tBu), 25.9 (3 x CH$_3$–tBu), 18.5 (C–tBu), 18.0 (C–tBu), −4.4 (CH$_3$–Me), −4.8 (CH$_3$–Me), −5.1 (CH$_3$–Me), −5.2 (CH$_3$–Me);

HRMS: (Cl, isobutane) for C$_{21}$H$_{45}$O$_4$Si$_2$ ([M+H]$^+$) calculated 417.2856, found 417.2852, $\Delta$ −0.9 ppm.
**Di-tert-butylsilyl-bis(trifluoromethanesulfonate)** (12.7 mL, 39.1 mmol) was added dropwise to a solution of diol 233 (5.03 g, 38.7 mmol) in anhydrous DMF (102 mL) at −45 ºC. The reaction mixture was stirred for 1 h at −45 ºC, then the reaction was quenched with pyridine (4.30 mL, 53.2 mmol). The solution was warmed to rt and diluted with Et$_2$O (125 mL). The organic phase was washed with H$_2$O (5 x 150 mL), dried (MgSO$_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et$_2$O, 99:1) afforded enol ether 231 (9.82 g, 94% yield) as a colourless solid.

$\text{R}_f = 0.91$ (petroleum ether–Et$_2$O, 1:1);

$\left[\alpha\right]_D (29.8 ^\circ \text{C}, \text{CHCl}_3) = +39.3$ (c = 1.03);

{Lit.$^{157}$ $\left[\alpha\right]_D (25 ^\circ \text{C}, \text{CHCl}_3) = +37.9$ (c = 1.10)};

m.p. = 38–40 ºC;

IR: $\nu_{\text{max}}$ 2933, 2860, 1653, 1473, 1387, 1239, 1129, 1078 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$ 6.26 (1H, ddd, $J = 5.9, 2.2, 1.4$ Hz, CH–C1), 4.69 (1H, ddd, $J = 5.9, 5.9, 2.2$ Hz, CH–C2), 4.18 (1H, dd, $J = 10.4, 4.8$ Hz, CH$_2$–C6), 4.11 (1H, ddd, $J = 9.6, 9.6, 5.9$ Hz, CH–C4), 3.92 (1H, dd, $J = 10.4, 10.4$ Hz, CH$_2$–C6), 3.71–3.65 (1H, m, CH–C5), 2.38 (1H, dddd, $J = 16.5, 5.9, 5.9, 1.4$ Hz, CH$_2$–C3), 2.07 (1H, dddd, $J = 16.5, 9.6, 2.2, 2.2$ Hz, CH$_2$–C3), 1.06 (9H, s, CH$_3$–tBu), 0.99 (9H, s, CH$_3$–tBu);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$C 142.7 (CH–C1), 99.0 (CH–C2), 74.1 (CH–C5), 71.5 (CH–C4), 66.5 (CH$_2$–C6), 30.3 (CH$_2$–C3), 27.6 (3 x CH$_3$–tBu), 27.1 (3 x CH$_3$–tBu), 22.9 (C–tBu), 20.0 (C–tBu);

HRMS: (EI’) for C$_{14}$H$_{26}$O$_3$Si ([M]$^+$) calculated 270.1651, found 270.1650, $\Delta$ −0.3 ppm.
(4aR,7aS)-2,2-Di-tert-butylhexahydroxireno[2’,3’:5,6]pyrano[3,2-d][1,3,2]dioxasiline (246)

A freshly distilled solution of dimethyl dioxirane (160 mL of a 0.1 M solution in acetone, 16.0 mmol) was added to a solution of enol ether 231 (3.32 g, 12.3 mmol) in anhydrous CH₂Cl₂ (160 mL) at −78 ºC. The reaction mixture was stirred for 1 h at −78 ºC. The solution was dried (MgSO₄) and concentrated under reduced pressure at 4 ºC to afford a diastereomeric mixture of epoxides 246 (3.52 g, dr 1.2:1) as a colourless solid. Epoxides 246 were then used without further purification.

(4aR,8aS)-6-Allyl-2,2-di-tert-butylhexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (248)

Allylmagnesium chloride (14.5 mL of a 1.7 M solution in Et₂O, 24.6 mmol) was added to a solution of epoxides 246 [12.3 mmol] in anhydrous THF (250 mL) at 0 ºC. The mixture was stirred for 1 h at 0 ºC and then the reaction was quenched with a saturated aqueous solution of NH₄Cl (200 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 150 mL). The organic extracts were combined, washed with brine (200 mL), dried (MgSO₄) and concentrated under reduced pressure to afford alcohols 248 as a mixture of diastereomers. The crude mixture was then used without further purification. (Purification was attempted on a small scale to separate the diastereomers. A small amount of the major diastereomer 247 was isolated and is characterised below.)
(4aR,6R,7S,8aS)-6-Allyl-2,2-di-tert-butylhexahydropyrano[3,2-d][1,3,2]dioxasilin-7-ol (247)

Rf = 0.52 (petroleum ether – Et2O, 1:1);
IR: \( \nu_{\text{max}} \) 3225, 2942, 2857, 1473, 1127, 1084, 1009 cm\(^{-1}\);
\(^1\)H NMR: (500 MHz, CDCl\(_3\)) \( \delta_H \) 5.77 (1H, dddd, \( J = 17.3, 10.4, 7.0, 7.0 \) Hz, CH-C8), 5.17–5.08 (2H, m, CH\(_2\)-C9), 4.13 (1H, ddd, \( J = 11.3, 9.6, 4.9 \) Hz, CH-C4), 4.01 (1H, dd, \( J = 10.0, 4.9 \) Hz, CH-C6), 3.89 (1H, m, CH-C2), 3.83 (1H, dd, \( J = 10.0, 10.0 \) Hz, CH\(_2\)-C6), 3.82–3.77 (1H, m, CH-C1), 3.54 (1H, ddd, \( J = 10.0, 9.6, 4.9 \) Hz, CH-C5), 2.61–2.49 (1H, m, CH\(_2\)-C7), 2.30 (1H, ddd, \( J = 14.3, 7.0, 7.0 \) Hz, CH\(_2\)-C7), 2.24–2.17 (1H, m, CH-C3), 1.74 (1H, ddd, \( J = 13.7, 11.3, 2.9 \) Hz, CH\(_2\)-C3), 1.03 (9H, s, CH\(_3\)-tBu), 0.99 (9H, s, CH\(_3\)-tBu);
\(^{13}\)C NMR: (126 MHz, CDCl\(_3\)) \( \delta_C \) 133.8 (CH-C8), 117.8 (CH\(_2\)-C9), 78.4 (CH-C1), 70.1 (CH-C5), 69.9 (CH-C4), 69.2 (CH-C2), 67.5 (CH\(_2\)-C6), 35.5 (CH\(_2\)-C7), 34.2 (CH\(_2\)-C3), 27.6 (3 x CH\(_3\)-tBu), 27.2 (3 x CH\(_3\)-tBu), 22.8 (C-tBu), 20.1 (C-tBu).

(4aR,8aS)-6-Allyl-2,2-di-tert-butyltetrahydropyrano[3,2-d][1,3,2]dioxasilin-7(6H)-one (249)

Sulfur trioxide pyridine complex (7.83 g, 49.2 mmol) and Et\(_3\)N (8.60 mL, 61.5 mmol) were added to a solution of alcohols 248 [12.3 mmol] in anhydrous CH\(_2\)Cl\(_2\):DMSO (1:1, 136 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, then diluted with Et\(_2\)O (150 mL). The mixture was washed with a solution of 1 M HCl (125 mL), a saturated aqueous solution of NaHCO\(_3\) (125 mL) and brine (125 mL). The organic phase was dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et\(_2\)O,
19:1) afforded a diastereomeric mixture of ketones 249 (2.86 g, 71% yield over three steps, dr 2.3:1) as a colourless solid. Ketones 249 were taken on to the next step without further purification. (Purification was attempted on a small scale to separate the diastereomers. The undesired diastereomer 249a was isolated and is characterised below.)

(4aR,6R,8aS)-6-Allyl-2,2-di-tert-butyltetrahydropyrano[3,2-d][1,3,2]dioxasilin-7(6H)-one (249a)

\[
\text{C}_{17}\text{H}_{31}\text{O}_{4}\text{Si} \\
\text{Molecular weight: 326.52 g.mol}^{-1}
\]

\[R_f = 0.86 \text{ (petroleum ether—Et}_2\text{O, 1:1)};\]
\[[\alpha]_D (26.5 \, ^\circ\text{C, CHCl}_3) = +80.0 \, (c = 0.99);\]
\[\text{m.p.} = 73-75 \, ^\circ\text{C};\]
\[\text{IR: } \nu_{\text{max}} 2932, 2859, 1722, 1474, 1238, 1109, 1067, 1007 \, \text{cm}^{-1};\]
\[\text{H NMR: (500 MHz, CDCl}_3 \text{)} \delta_H 5.76 \, (1\text{H, dddd, } J = 16.9, 9.8, 7.0, 7.0 \, \text{Hz, CH-C8}),\]
5.18–5.15 (1H, m, CH2-C9), 5.15–5.13 (1H, m, CH2-C9), 4.17 (1H, dd, J = 10.2, 4.8 Hz, CH2-C6), 4.15–4.12 (1H, m, CH-C4), 4.06 (1H, dd, J = 9.8, 5.5 Hz, CH-C1), 3.87 (1H, dd, J = 10.2, 10.2 Hz, CH2-C6), 3.76 (1H, ddd, J = 10.2, 9.7, 4.8 Hz, CH-C5), 2.97 (1H, dd, J = 16.4, 5.6 Hz, CH2-C3), 2.65–2.57 (1H, m, CH2-C7), 2.48 (1H, dd, J = 16.4, 11.1 Hz, CH2-C3), 2.41 (1H, ddd, J = 13.4, 6.7, 5.5 Hz, CH2-C7), 1.05 (9H, s, CH3-tBu), 1.01 (9H, s, CH3-tBu);
\[\text{C NMR: (126 MHz, CDCl}_3 \text{)} \delta_C 207.1 \, (\text{C-C2}), 132.5 \, (\text{CH-C8}), 118.7 \, (\text{CH2-C9}), 81.1 \, (\text{CH-C1}), 72.7 \, (\text{CH-C4}), 69.7 \, (\text{CH-C5}), 67.1 \, (\text{CH2-C6}), 46.4 \, (\text{CH2-C3}), 34.3 \, (\text{CH2-C7}), 27.6 \, (3 \times \text{CH3-tBu}), 27.2 \, (3 \times \text{CH3-tBu}), 22.8 \, (\text{C-tBu}), 20.1 \, (\text{C-tBu});\]
\[\text{HRMS: (Cl, isobutane) for C}_{17}\text{H}_{31}\text{O}_{4}\text{Si ([M+H]}^+ \text{) calculated 327.1992, found 327.1996, } \Delta +1.2 \, \text{ppm.}\]
DBU (0.30 mL, 2.0 mmol) was added to a solution of ketones 249 (2.58 g, 7.90 mmol) in anhydrous toluene (92 mL) at rt. The reaction mixture was stirred for 24 h in the dark, then the reaction was quenched with a saturated aqueous solution of NH₄Cl (85 mL). The two phases were separated and the aqueous phase extracted with Et₂O (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 99:1) afforded the desired ketone 250 (1.55 g, 60% yield) as a colourless solid

\[ R_f = 0.86 \text{ (petroleum ether—Et}_2\text{O, 1:1)}; \]
\[ [\alpha]_D(27.5 \degree C, \text{CHCl}_3) = -22.0 \text{ (c = 1.16)}; \]
\{Lit.\[116] \[\alpha\]_D(24.5 \degree C, \text{CHCl}_3) = -24.1 \text{ (c = 1.07)}; \}
m.p. = 83—85 \degree C;
IR: \nu_{max} 2934, 2861, 1724, 1476, 1364, 1146, 1115, 1099 cm\(^{-1}\);
\(^1\)H NMR: (500 MHz, CDCl\(_3\)) \(\delta\)H 5.80 (1H, dddd, \(J = 17.1, 10.2, 7.0, 7.0 \text{ Hz, CH-C8}), 5.11 (1H, dddd, \(J = 17.1, 1.7, 1.4, 1.4 \text{ Hz, CH}_2\text{-C9}), 5.08–5.03 (1H, m, CH-C9), 4.26 (1H, dd, \(J = 10.3, 5.0 \text{ Hz, CH}_2\text{-C6}), 4.12 (1H, ddd, \(J = 11.1, 9.4, 5.7 \text{ Hz, CH-C4}), 3.90 (1H, dd, \(J = 10.3, 10.3 \text{ Hz, CH}_2\text{-C6}), 3.85 (1H, dd, \(J = 7.6, 4.3 \text{ Hz, CH-C1}), 3.61 (1H, ddd, \(J = 10.3, 9.4, 5.0 \text{ Hz, CH-C5}), 3.01 (1H, dd, \(J = 15.7, 5.7 \text{ Hz, CH}_2\text{-C3}), 2.65–2.58 (1H, m, CH}_2\text{-C7), 2.45 (1H, dd, \(J = 15.7, 11.1 \text{ Hz, CH}_2\text{-C3), 2.30 (1H, ddd, \(J = 14.6, 7.6, 7.0 \text{ Hz, CH}_2\text{-C7), 1.05 (9H, s, CH}_3\text{-tBu), 1.01 (9H, s, CH}_3\text{-tBu); \}
\(^13\)C NMR: (126 MHz, CDCl\(_3\)) \(\delta\)C 204.8 (C-C2), 133.8 (CH-C8), 117.7 (CH-C9), 82.7 (CH-C1), 76.5 (CH-C5), 73.3 (CH-C4), 66.7 (CH-C6), 48.4 (CH-C3), 33.6 (CH-C7), 27.6 (3x CH\(_3\)-tBu), 27.2 (3x CH\(_3\)-tBu), 22.8 (C-tBu), 20.1 (C-tBu);
HRMS: (Cl, isobutane) for C\(_{17}\)H\(_{31}\)O\(_4\)Si ([M+H]\(^+\)) calculated 327.1992, found 327.1993, \(\Delta = +0.4 \text{ ppm.} \)
(4aR,6S,7R,8aS)-6-Allyl-2,2-di-tert-butylhexahydropyranono[3,2-d][1,3,2]dioxasilin-7-ol (251)

Sodium borohydride (984 mg, 26.0 mmol) was added to a solution of ketone 250 (2.12 g, 6.50 mmol) in anhydrous CH₂Cl₂:MeOH (1:1, 232 mL) at -78 °C. The reaction mixture was stirred for 2 h at -78 °C and then the reaction was quenched with a saturated aqueous solution of NH₄Cl (150 mL). The two phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 100 mL). The organic extracts were combined, washed with brine (175 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 17:1 to 7:3) afforded alcohol 251 (1.89 g, 88% yield) as a colourless solid.

R_f = 0.74 (petroleum ether—Et₂O, 1:1);
[α]_D (25.6 °C, CHCl₃) = +25.1 (c = 1.02);
{Lit.¹²⁰ [α]_D (29 °C, CHCl₃) = +27.3 (c = 1.00)};
m.p. = 65–67 °C;
IR: ν_max 3382, 2835, 2861, 2362, 1474, 1360, 1092, 1033, 1010 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δ_H 5.90 (1H, dddd, J = 17.2, 10.2, 7.0, 7.0 Hz, CH-C8), 5.13 (1H, dddd, J = 17.2, 1.8, 1.6, 1.6 Hz, CH₂-C9), 5.09–5.07 (1H, m, CH₂-C9), 4.13 (1H, dd, J = 10.2, 5.0 Hz, CH₂-C6), 3.79 (1H, dd, J = 10.2, 10.2 Hz, CH₂-C6), 3.78–3.73 (1H, m, CH-C4), 3.50–3.44 (1H, m, CH-C2), 3.27 (1H, ddd, J = 10.2, 9.2, 5.0 Hz, CH-C5), 3.19 (1H, ddd, J = 9.5, 7.2, 4.0 Hz, CH-C1), 2.57–2.51 (1H, m, CH₂-C7), 2.46 (1H, ddd, J = 11.6, 5.0, 4.5 Hz, CH₂-C3), 2.27 (1H, ddd, J = 14.3, 7.2, 7.0 Hz, CH₂-C7), 1.55 (1H, d, J = 4.5 Hz, OH), 1.49 (1H, app q, J = 11.6 Hz, CH₂-C3), 1.04 (9H, s, CH₃-tBu), 0.99 (9H, s, CH₃-tBu);
¹³C NMR: (126 MHz, CDCl₃) δ_C 134.8 (CH-C8), 117.3 (CH₂-C9), 81.5 (CH-C1), 77.3 (CH-C5), 72.5 (CH-C4), 69.5 (CH₂-C2), 67.0 (CH₂-C6), 42.0 (CH₂-C3), 36.6 (CH₂-C7), 27.6 (3 x CH₃-tBu), 27.2 (3 x CH₃-tBu), 22.8 (C-tBu), 20.1 (C-tBu);
HRMS: (Cl, isobutane) for C₁₇H₃₃O₄Si ([M+H]⁺) calculated 329.2148, found 329.2154, Δ +1.7 ppm.
2-Bromo-N-methoxy-N-methylacetamide\textsuperscript{158}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{O}};
\node at (-0.5,0.5) {\text{Br}};
\node at (0,0.5) {\text{O}};
\node at (0.5,0.5) {\text{N}};
\node at (0.5,0.75) {\text{O}};
\node at (0.5,1.25) {\text{N}};
\end{tikzpicture}
\end{center}

\text{C}_4\text{H}_8\text{BrNO}_2 \hspace{2cm}
\text{Molecular weight: 182.02 g.mol}^{-1}

An ice-cooled solution of $\text{K}_2\text{CO}_3$ (6.24 g, 45.0 mmol) in $\text{H}_2\text{O}$ (25 mL) was added to a solution of $\text{N}$-methylhydroxylamine hydrochloride (2.00 g, 20.5 mmol) in $\text{Et}_2\text{O}$ (25 mL) at 0 °C. Bromoacetyl bromide (2.14 mL, 24.6 mmol) was added dropwise and the reaction mixture stirred for 30 min at rt. The phases were separated and the aqueous phase extracted with $\text{Et}_2\text{O}$ (3 x 50 mL). The organic extracts were combined, washed with brine (75 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was distilled under reduced pressure (100 °C, 30 mbar) to afford 2-bromo-$\text{N}$-methoxy-$\text{N}$-methylacetamide (2.42 g, 65% yield) as a colourless oil.

$R_f = 0.27$ (petroleum ether--$\text{Et}_2\text{O}$, 1:1);
IR: $\nu_{\text{max}}$ 2977, 2942, 1668, 1462, 1431, 1386, 1180 cm$^{-1}$;
$^1\text{H NMR}$: (500 MHz, CDCl$_3$) $\delta_H$ 3.99 (2H, s, CH$_2$–C2), 3.77 (3H, s, CH$_3$–C4), 3.22 (3H, s, CH$_3$–C3);
$^{13}\text{C NMR}$: (126 MHz, CDCl$_3$) $\delta_C$ 167.8 (C–C1), 61.8 (CH$_3$–C4), 32.7 (CH$_2$–C2), 25.2 (CH$_3$–C3).

2-[[(4aR,6S,7R,8aS)-6-Allyl-2,2-di-tert-butylhexahydropyran[3,2-d][1,3,2]dioxasilin-7-yl]oxy]-$\text{N}$-methoxy-$\text{N}$-methylacetamide (271)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{O}};
\node at (-0.5,0.5) {\text{O}};
\node at (0,0.5) {\text{N}};
\node at (0.5,0.5) {\text{O}};
\node at (0.5,0.75) {\text{O}};
\node at (0.5,1.25) {\text{N}};
\end{tikzpicture}
\end{center}

\text{C}_{21}\text{H}_{39}\text{NO}_6\text{Si}
\hspace{2cm}
\text{Molecular weight: 429.62 g.mol}^{-1}

KHMD$\text{S}$ (0.69 mL of 0.5 $\text{M}$ solution in THF, 0.35 mmol) was added to a solution of 230 (100 mg, 0.300 mmol) in anhydrous THF (1.5 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 5 min, then cooled to −78 °C. 2-Bromo-$\text{N}$-methoxy-$\text{N}$-methylacetamide (81.9 mg, 0.450 mmol) in anhydrous THF (1 mL)
was added dropwise and the reaction mixture stirred for 3 h at −78 °C, then overnight at rt. The reaction was quenched with a saturated aqueous solution of NH₄Cl (2 mL) then diluted with H₂O (5 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 10 mL). The organic extracts were combined, washed with brine (15 mL), dried (MgSO₄) and concentrated under reduced pressure. NaOAc (66.0 mg, 0.800 mmol) was added to a solution of crude residue 271 [0.300 mmol] in DMSO (3 mL). The reaction mixture was stirred for 1.5 h at rt, then diluted with Et₂O (5 mL) and washed with H₂O (3 x 5 mL). The phases were separated and the organic phase was dried (MgSO₄) then concentrated under reduced pressure to afford amide 271 (43.0 mg, 32% yield) as a colourless oil and alcohol 230 (64.0 mg, 50% recovered starting material).

Rᵥ = 0.44 (petroleum ether–Et₂O, 1:1);  
[α]D (27.1 °C, CHCl₃) = −49.5 (c = 1.00);  
IR: ν max 2934, 2860, 2363, 1692, 1473, 1092, 1033, 1000 cm⁻¹;  
¹H NMR: (500 MHz, CDCl₃) δH 5.87 (1H, dddd, J = 17.1, 10.2, 7.0, 7.0 Hz, CH–C8), 5.09 (1H, dddd, J = 17.1, 1.8, 1.5, 1.5 Hz, CH₂–C9), 5.05–5.01 (1H, m, CH₂–C9), 4.34 (1H, d, J = 15.5 Hz, CH₂–C10), 4.29 (1H, d, J = 15.5 Hz, CH₂–C10), 4.11 (1H, dd, J = 10.2, 4.9 Hz, CH₂–C6), 3.77 (1H, dd, J = 10.2, 10.2 Hz, CH₂–C6), 3.74–3.69 (1H, m, CH–C4), 3.68 (3H, s, CH₃–C13), 3.36–3.31 (1H, m, CH–C5), 3.30–3.24 (2H, m, CH–C1, CH–C2), 3.18 (3H, s, CH₃–C12), 2.72–2.66 (1H, m, CH₂–C7), 2.64 (1H, ddd, J = 11.7, 4.4, 4.4 Hz, CH₂–C3), 2.23 (1H, ddd, J = 14.9, 7.0, 7.0 Hz, CH₂–C7), 1.49 (1H, ddd, J = 11.7, 11.4, 11.3 Hz, CH₂–C3), 1.02 (9H, s, CH₃–tBu), 0.97 (9H, s, CH₃–tBu);  
¹³C NMR: (126 MHz, CDCl₃) δC 170.8 (C–C11), 135.1 (CH–C8), 116.9 (CH₂–C9), 80.3 (CH–C5), 77.2 (CH–C1), 76.9 (CH–C2), 72.6 (CH–C4), 67.0 (CH₂–C6), 66.2 (CH₂–C10), 61.6 (CH₃–C13), 38.2 (CH₂–C3), 36.1 (CH₂–C7), 32.4 (CH₃–C12), 27.6 (3 x CH₃–tBu), 27.2 (3 x CH₃–tBu), 22.7 (C–tBu), 20.1 (C–tBu);  
HRMS: (ESI) for C₂₁H₃₉NNaO₆Si ([M+Na]⁺) calculated 452.2444, found 452.2439, Δ = −0.2 ppm.
tert-Butyl-2-([(4aR,6S,7R,8aS)-6-allyl-2,2-di-tert-butylhexahydropyrano[3,2-d][1,3,2]dioxasilin-7-yl]oxy]acetate (269)\(^{157}\)

A 30% aqueous solution of NaOH (2 mL) was added to a solution of 230 (100 mg, 0.300 mmol) in toluene (2 mL) at 0 °C. After 5 min, tert-butyl bromoacetate (0.09 mL, 0.6 mmol) and TBAI (55.0 mg, 0.150 mmol) were added and the reaction mixture stirred overnight at rt. The solution was diluted with toluene (5 mL) and H\(_2\)O (5 mL), then the two phases were separated and the aqueous phase extracted with toluene (3 x 10 mL). The organic extracts were combined, washed with 1 M HCl (10 mL) and brine (15 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et\(_2\)O, 19:1) afforded ester 269 (109 mg, 82% yield) as a colourless oil.

\(R_f = 0.84 \text{ (petroleum ether—Et}_2\text{O, 1:1)};\)

\([\alpha]_{D}^25.1 \degree \text{C, CHCl}_3 = -31.0 \text{ (c = 1.49)};\)

IR: ν\(_{max}\) 2933, 2860, 1751, 1474, 1368, 1225, 1090 cm\(^{-1}\);

\(^1\)H NMR: (500 MHz, CDCl\(_3\)) δ\(_H\) 5.88 (1H, dddd, 17.2, 10.2, 6.9, 6.9 Hz, CH-C8), 5.10 (1H, dddd, 17.2, 1.9, 1.5, 1.5 Hz, CH-C9), 5.06–5.02 (1H, m, CH-C9), 4.12 (1H, dd, 10.2, 4.9 Hz, CH-C6), 4.03 (1H, d, 16.1 Hz, CH-C10), 3.98 (1H, d, 16.1 Hz, CH-C10), 3.78 (1H, dd, 10.2, 10.2 Hz, CH-C6), 3.71 (1H, ddd, 17.2, 9.2, 4.5 Hz, CH-C4), 3.33–3.25 (2H, m, CH-C1, CH-C5), 3.21 (1H, ddd, 10.9, 9.2, 4.5 Hz, CH-C2), 2.72–2.66 (1H, m, CH-C7), 2.60 (1H, ddd, 11.8, 4.5, 4.5 Hz, CH-C3), 2.22 (1H, ddd, 15.0, 7.6, 6.9 Hz, CH-C7), 1.48 (9H, s, CH\(_3\)-C13), 1.52–1.43 (1H, m, CH-C2), 1.03 (9H, s, CH\(_3\)-tBu), 0.98 (9H, s, CH\(_3\)-tBu);

\(^{13}\)C NMR: (126 MHz, CDCl\(_3\)) δ\(_C\) 169.5 (C-C11), 135.1 (CH-C8), 116.9 (CH\(_2\)-C9), 81.9 (C-C12), 80.3 (CH-C5), 77.2 (CH-C1), 76.9 (CH-C2), 72.5 (CH-C4), 67.0 (CH\(_2\)-C6), 66.8 (CH\(_2\)-C10), 38.3 (CH\(_2\)-C3), 36.2 (CH\(_2\)-C7), 28.3 (3 \times CH\(_3\)-C13), 27.6 (3 \times CH\(_3\)-tBu), 27.2 (3 \times CH\(_3\)-tBu), 22.8 (C-tBu), 20.1 (C-tBu);
HRMS: (EI′) for \( \text{C}_{23}\text{H}_{42}\text{O}_{6}\text{Si} \) ([M]′) calculated 442.2751, found 442.2738, \( \Delta -2.9 \) ppm.

2-\{[(4aR,6S,7R,8aS)-6-Allyl-2,2-di-tert-butylhexahydropyrano[3,2-d][1,3,2]dioxasilin-7-yl]oxy}acetaldehyde (270)

\[
\text{C}_{19}\text{H}_{34}\text{O}_{5}\text{Si}
\]

Molecular weight: 370.56 g mol\(^{-1}\)

DIBAL (0.46 mL of a 1 m solution in CH\(_2\)Cl\(_2\), 0.46 mmol) was added to a solution of 269 (99.7 mg, 0.230 mmol) in anhydrous CH\(_2\)Cl\(_2\) (2 mL) at \(-78^\circ\text{C}\). The reaction mixture was stirred for 3 h at \(-78^\circ\text{C}\), then diluted with MeOH (4 mL) and 1 m HCl (4 mL). The two phases were separated and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The organic extracts were combined, washed with a 5% aqueous solution of NaHCO\(_3\) (20 mL) and brine (20 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. The crude aldehyde 270 was then used without further purification.

1-\{[(4aR,6S,7R,8aS)-6-Allyl-2,2-di-tert-butylhexahydropyrano[3,2-d][1,3,2]dioxasilin-7-yl]oxy}but-3-en-2-ol (267)

\[
\text{C}_{21}\text{H}_{38}\text{O}_{5}\text{Si}
\]

Molecular weight: 398.61 g mol\(^{-1}\)

Vinylmagnesium bromide (0.46 mL of a 1 m solution in THF, 0.46 mmol) was added to a solution of crude aldehyde 270 [0.230 mmol] in anhydrous THF (5 mL) at 0 °C. The mixture was stirred for 45 min at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH\(_4\)Cl (7 mL). The phases
were separated and the aqueous phase extracted with Et₂O (3 x 15 mL). The organic extracts were combined, washed with brine (25 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 4:1) afforded an inseparable mixture of the diastereomeric alcohols 267 (80.0 mg, 87% over two steps, dr 1:1) as a colourless oil.

Rₜ = 0.76 (petroleum ether–Et₂O, 1:1);
IR: vₘₐₓ 3459, 2934, 2860, 1474, 1365, 1089, 1010 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δH 5.91–5.79 (4H, m, CH-C8/C8′ and CH-C12/12′), 5.36 (2H, ddd, J = 17.3, 3.5, 1.6 Hz, CH₂-C13/C13′), 5.21 (2H, d, J = 10.6 Hz, CH₂-C13/C13′), 5.12–5.03 (4H, m, CH₂-C9/C9′), 4.27 (2H, br s, CH-C11/C11′), 4.12 (2H, dd, J = 10.2, 4.9 Hz, CH₂-C6/C6′), 3.78 (2H, dd, J = 10.2, 10.2 Hz, CH₂-C6/C6′), 3.72 (2H, dddd, J = 13.8, 9.3, 4.6, 2.5 Hz, CH-C4/C4′), 3.68 (1H, dd, J = 9.4, 3.5 Hz, CH₂-C10), 3.51 (1H, dd, J = 9.4, 7.5 Hz, CH₂-C10′), 3.44 (1H, dd, J = 9.4, 3.7 Hz, CH₂-C10′), 3.32–3.23 (5H, m, CH-C1/C1′ and CH-C5/C5′ and CH₂-C10), 3.18 (2H, dddd, J = 11.4, 9.2, 4.4, 2.5 Hz, CH-C2/C2′), 2.61 (2H, ddd, J = 12.0, 8.0, 4.4 Hz, CH₂-C3/C3′), 2.57–2.51 (2H, m, CH₂-C7/C7′), 2.32 (1H, d, J = 3.5 Hz, OH), 2.26 (1H, d, J = 3.7 Hz, OH), 2.25–2.19 (2H, m, CH₂-C7/C7′), 1.48–1.38 (2H, m, CH₂-C3/C3′), 1.03 (18H, s, CH₃-tBu), 0.98 (18H, s, CH₃-tBu);
¹³C NMR: (126 MHz, CDCl₃) δC 136.7 and 136.6 (CH-C12/12′), 134.9 and 134.8 (CH-C8/C8′), 117.0 and 116.9 (CH₂-C9/C9′), 116.8 (CH₂-C13/C13′), 80.0 (CH-C1/C1′), 77.2 (CH-C5/C5′), 76.5 (CH-C2/C2′), 72.8 and 72.6 (CH₂-C10/C10′), 72.5 and 72.4 (CH-C4/C4′), 72.0 and 71.7 (CH-C11/C11′), 67.0 (CH₂-C6/C6′), 38.6 and 38.4 (CH₂-C3/C3′), 36.5 and 36.4 (CH₂-C7/C7′), 27.6 (6 x CH₃-tBu), 27.2 (6 x CH₃-tBu), 22.8 (2 x C-tBu), 20.1 (2 x C-tBu);
HRMS: (EI⁺) for C₂₁H₃₈O₅Si ([M⁺]⁺) calculated 398.2489, found 398.2489, Δ +0.2 ppm.
Dess-Martin periodinane (212 mg, 0.500 mmol) was added to a solution of the alcohols 267 (100 mg, 0.250 mmol) in CH₂Cl₂ (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then the reaction was quenched with a solution of saturated aqueous NaHCO₃ and Na₂S₂O₃ (1:1, 20 mL). The phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 15 mL). The organic extracts were combined, washed with brine (25 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 9:1) afforded enone 229 (90.6 mg, 92% yield) as a colourless solid.

Rᵥ = 0.74 (petroleum ether—Et₂O, 1:1);
[α]₀ (26.9 °C, CHCl₃) = −51.4 (c = 0.96);
m.p. = 39—41 °C;
IR: νₘₐₓ 2934, 2860, 1703, 1614, 1474, 1090 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δH 6.54 (1H, dd, J = 17.6, 10.7 Hz, CH–C₁₂), 6.35 (1H, dd, J = 17.6, 1.2 Hz, CH₂–C₁₃), 5.91—5.82 (2H, m, CH–C₈ and CH₂–C₁₃), 5.11—5.03 (2H, m, CH₂–C₉), 4.35 (1H, d, J = 16.6 Hz, CH₂–C₁₀), 4.24 (1H, d, J = 16.6 Hz, CH₂–C₁₀), 4.12 (1H, dd, J = 10.2, 5.0 Hz, CH₂–C₆), 3.77 (1H, dd, J = 10.2, 10.2 Hz, CH₂–C₆), 3.71 (1H, ddd, J = 11.2, 9.2, 4.4 Hz, CH–C₄), 3.37—3.33 (1H, m, CH–C₁), 3.28 (1H, ddd, J = 10.2, 9.2, 5.0 Hz, CH–C₅), 3.21 (1H, ddd, J = 11.0, 9.2, 4.5 Hz, CH–C₂), 2.66—2.61 (1H, m, CH₂–C₇), 2.61—2.56 (1H, m, CH₂–C₃), 2.24 (1H, ddd, J = 14.9, 7.4, 7.4 Hz, CH–C₇), 1.48 (1H, app q, J = 11.2 Hz, CH₂–C₃), 1.02 (9H, s, CH₃–tBu), 0.97 (9H, s, CH₃–tBu);
¹³C NMR: (126 MHz, CDCl₃) δC 196.7 (C–C₁₁), 134.7 (CH–C₈), 132.5 (CH–C₁₂), 129.5 (CH₂–C₁₃), 117.1 (CH₂–C₉), 80.0 (CH–C₁), 77.2 (CH–C₅), 77.0 (CH–C₂), 73.0 (CH₂–C₁₀), 72.5 (CH–C₄), 67.0 (CH₂–C₆), 38.2 (CH₂–C₃), 36.2 (CH₂–C₇), 27.6 (3 x CH₃–tBu), 27.2 (3 x CH₃–tBu), 22.8 (C–tBu), 20.1 (C–tBu);
HRMS: (ESI) for C_{21}H_{36}NaO_{5}Si ([M+Na]^{+}) calculated 419.2230, found 419.2224, Δ +3.3 ppm.

\((E)-1\-\{(4aR,6S,7R,8aS)-6\-Allyl-2,2-di-tert-butylhexahydropyrano[3,2-d][1,3,2]dioxasilin-7-yl\}oxy\}hept-3-en-2-one (272)

\[
\begin{align*}
C_{24}H_{42}O_{5}Si \\
\text{Molecular weight: 438.67 g.mol}^{-1}
\end{align*}
\]

To a suspension of sodium hydride (146 mg of a 60% suspension in mineral oil, 6.08 mmol) in anhydrous THF (25 mL) at 0 °C was added a solution of 230 (500 mg, 1.52 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred at 0 °C for 10 min then warmed to rt before triphenylchloroacetonylphosphorane (642 mg, 1.82 mmol) and TBAI (28.0 mg, 0.0760 mmol) were added. The reaction mixture was heated to reflux and stirred for 3 h. The solution was cooled to rt, and the reaction was quenched with H_{2}O (10 mL) and concentrated under reduced pressure. The phases were separated and the aqueous phase extracted with EtOAc (4 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried (MgSO_{4}) and concentrated under reduced pressure. The crude phosphorane 262 was isolated as a yellow foam and used without further purification.

Butyraldehyde (1.40 mL, 15.2 mmol) was added to a solution of crude phosphorane 262 [1.52 mmol] in anhydrous CH_{2}Cl_{2} (50 mL). The reaction mixture was heated to reflux and stirred overnight. Further butyraldehyde (1.40 mL, 15.2 mmol, 10 equiv.) was added and the reaction mixture stirred at reflux for 24 h. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether–Et_{2}O, 19:1) to afford enone 272 (573 mg, 86% yield over two steps) as a yellow oil.
$R_f = 0.85$ (petroleum ether–Et$_2$O, 1:1);
$[\alpha]_D$ (26.1 °C, CHCl$_3$) = −52.0 ($c = 0.97$);
IR: $\nu_{\text{max}}$ 2961, 2933, 2860, 1696, 1625, 1473, 1089, 1055 cm$^{-1}$;
$^1$H NMR: (500 MHz, CDCl$_3$) $\delta_H$ 6.97 (1H, ddd, $J = 15.8$, 7.0, 7.0 Hz, CH-C13), 6.28 (1H, ddd, $J = 15.8$, 1.5, 1.5 Hz, CH-C12), 5.87 (1H, dddd, $J = 17.1$, 10.2, 6.9, 6.9 Hz, CH-C8), 5.08 (1H, dddd, $J = 17.1$, 1.8, 1.6, 1.6 Hz, CH$_2$-C9), 5.06–5.03 (1H, m, CH$_2$-C9), 4.29 (1H, d, $J = 16.3$ Hz, CH$_2$-C10), 4.18 (1H, d, $J = 16.3$ Hz, CH$_2$-C10), 4.12 (1H, dd, $J = 10.2$, 4.9 Hz, CH$_2$-C6), 3.78 (1H, dd, $J = 10.2$, 10.2 Hz, CH$_2$-C6), 3.71 (1H, ddd, $J = 11.2$, 9.2, 4.5 Hz, CH-C4), 3.35 (1H, ddd, $J = 9.2$, 7.8, 3.1 Hz, CH-C1), 3.32–3.26 (1H, m, CH-C5), 3.21 (1H, ddd, $J = 11.4$, 9.2, 4.5 Hz, CH-C2), 2.67–2.61 (1H, m, CH$_2$-C7), 2.59 (1H, ddd, $J = 11.4$, 4.5, 4.5 Hz, CH$_2$-C3), 2.27–2.19 (3H, m, CH$_2$-C7 and CH$_2$-C14), 1.55–1.43 (3H, m, CH$_2$-C15 and CH$_2$-C3), 1.03 (9H, s, CH$_3$-tBu), 0.98 (9H, s, CH$_3$-tBu), 0.95 (3H, t, $J = 7.4$ Hz, CH$_3$-C16);
$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta_C$ 196.6 (C-C11), 149.0 (CH-C13), 134.8 (CH-C8), 126.2 (CH-C12), 117.1 (CH$_2$-C9), 80.1 (CH-C2), 77.2 (CH-C5), 76.9 (CH-C1), 73.1 (CH$_2$-C10), 72.5 (CH-C4), 67.0 (CH$_2$-C6), 38.2 (CH$_2$-C3), 36.2 (CH$_2$-C7), 34.8 (CH$_2$-C14), 27.6 (3 x CH$_3$-tBu), 27.2 (3 x CH$_3$-tBu), 22.8 (C-tBu), 21.4 (CH$_2$-C15), 20.1 (C-tBu), 13.9 (CH$_3$-C16);
HRMS: (EI') for C$_{24}$H$_{42}$O$_5$Si ([M]$^+$) calculated 438.2802, found 438.2805, $\Delta +0.8$ ppm.
(E)-1-[[((4aR,6S,7R,8aS)-6- Allyl-2,2-di-tert-butyldihexahydropyrano[3,2-d][1,3,2]dioxasilin-7-yloxy)hept-3-en-2-ol (273)

Cerium trichloride heptahydrate (484 mg, 1.30 mmol) and sodium borohydride (60.0 mg, 1.56 mmol) were added to a solution of enone 272 (570 mg, 1.30 mmol) in MeOH (70 mL) at −78 ºC. The reaction mixture was stirred for 1.5 h at −78 ºC, then the reaction was quenched with a saturated aqueous solution of NH₄Cl (75 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 50 mL). The organic extracts were combined, washed with brine (125 mL), dried (MgSO₄) and concentrated under reduced pressure to afford an inseparable mixture of the diastereomeric alcohols 273 (533 mg, 93% yield, dr 1:1) as a colourless oil.

R_f = 0.76 (petroleum ether–Et₂O, 1:1);
IR: ν_{max} 3457, 2934, 2861, 2364, 1474, 1365, 1092, 1012 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δ_H 5.91–5.81 (2H, m, CH-C8/C8'), 5.81–5.73 (2H, m, CH-13/C13'), 5.43 (1H, ddd, J = 6.7, 2.7, 1.3 Hz, CH-C12), 5.40 (1H, ddd, J = 6.7, 2.7, 1.3 Hz, CH-C12'), 5.11–5.03 (4H, m, CH₂-C9/C9'), 4.26–4.19 (2H, m, CH₂-C11/C11'), 4.11–4.04 (4H, m, CH₂-C6/C6'), 3.78 (2H, dd, J = 10.2, 4.9 Hz, CH₂-C6/C6'), 3.75–3.69 (2H, m, CH₂-C4/C4'), 3.63 (1H, dd, J = 10.2, 10.2 Hz, CH₂-C6/C6'), 3.51–3.46 (1H, m, CH₂-C10), 3.39 (1H, dd, J = 9.4, 3.2 Hz, CH₂-C10'), 3.28 (4H, m, CH-C5/C5' and CH-C1/C1'), 3.23 (1H, dd, J = 9.4, 8.2 Hz, CH₂-C10), 3.21–3.14 (2H, m, CH₂-C2/C2'), 2.61 (2H, app dq, J = 11.8, 4.6 Hz, CH₂-C3/C3'), 2.54 (2H, m, CH₂-C7/C7'), 2.39 (1H, d, J = 3.0 Hz, CH₂-C10'), 2.27–2.22 (2H, m, CH₂-C7/C7'), 2.21 (1H, d, J = 3.2 Hz, OH), 2.02 (4H, dd, J = 14.5, 7.3 Hz, CH₂-C14/C14'), 1.48–1.36 (6H, m, CH₂-C3/C3' and CH₂-C15/C15'), 1.03 (18H, s, CH₃-tBu), 0.98 (18H, s, CH₃-tBu), 0.90 (6H, 2 x t, J = 7.4 Hz and J = 7.4 Hz, CH₃-C16/C16');
¹³C NMR: (126 MHz, CDCl₃) δ_C 134.9 and 134.8 (CH-C8/C8'), 134.2 and 134.1 (CH-C13/C13'), 128.3 and 128.2 (CH-C12/C12'), 117.0 and 116.9 (CH₂-C9/C9'),
80.1 and 80.0 (CH-C5/C5'), 77.3 (2 x CH-C1/C1'), 76.5 (2 x CH-C2/C2'), 73.3 and 73.0 (CH-C10/C10'), 72.6 and 72.5 (CH-C4/C4'), 71.9 and 71.5 (CH-C11/C11'), 67.0 (CH2-C6/C6'), 38.7 and 38.4 (CH2-C3/C3'), 36.5 and 34.6 (CH2-C7/C7'), 27.6 (6 x CH3-tBu), 27.2 (6 x CH3-tBu), 22.8 (2 x C-tBu), 22.3 (CH2-C15/C15'), 20.1 (2 x C-tBu), 13.8 (2 x CH3-C16/16');

HRMS: (EI') for C24H44O5Si ([M]+) calculated 440.2958, found 440.2960, Δ +0.4 ppm.

(4aR,5aS,11aR,12aS,Z)-2,2-Di-tert-butyl-4a,5a,6,9,10,11a,12,12a-octahydro-4H-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-b]oxocin-9-ol (268)

Hoveyda-Grubbs second generation catalyst 150 (21.0 mg, 0.0340 mmol) was added to a solution of 273 (299 mg, 0.680 mmol) in degassed anhydrous CH2Cl2 (680 mL). The reaction mixture was heated to reflux and stirred overnight. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et2O, 4:1) to afford an inseparable mixture of the diastereomeric alcohols 268 (240 mg, 96% yield, dr 1:1) as a colourless oil.

Rf = 0.41 (petroleum ether—Et2O, 1:1);

IR: νmax 3318, 2932, 2859, 1474, 1366, 1101, 1061, 1042 cm⁻¹;

1H NMR: (500 MHz, CDCl₃) δH 5.86—5.75 (2H, m, CH-C8 and CH-C9'), 5.71—5.64 (1H, m, CH-C8'), 5.59 (1H, ddd, J = 10.7, 7.2, 1.3 Hz, CH-C9), 4.71—4.63 (1H, m, CH-C10), 4.58—4.52 (1H, m, CH-C10'), 4.13—4.08 (2H, m, CH2-C6/C6'), 3.87 (1H, dd, J = 11.6, 3.8 Hz, CH2-C11'), 3.74 (2H, dd, J = 10.2, 10.2 Hz, CH2-C6/C6'), 3.69—3.63 (3H, m, CH2-C11 and CH-C4/C4'), 3.42—3.34 (3H, m, CH2-C11' and CH-C1' and CH-C2'), 3.31—3.11 (5H, m, CH2-C11 and CH-C5/C5' and CH-C1 and CH-C2), 2.70—2.63 (1H, m, CH2-C7'), 2.45 (1H, ddd, J = 13.2, 8.7, 2.8 Hz, CH2-C7), 2.39 (1H, app dt, J = 11.5, 4.3 Hz, CH2-C3 or C3'), 2.36—2.29 (2H, m,
CH₂-C3 or 3’ and CH₂-C7’), 2.25–2.17 (1H, m, CH₂-C7), 1.58–1.46 (2H, m, CH₂-C3/C3’), 1.02 (18H, s, CH₃-tBu), 0.97 (18H, s, CH₃-tBu);

¹³C NMR: (126 MHz, CDCl₃) δC 137.4 and 134.1 (CH-C9/C9’), 126.6 and 126.4 (CH-C8/C8’), 83.0 (CH-C2 or CH-C1), 79.7 and 79.4 (CH-C1’ and CH-C2’), 78.0 and 77.3 (CH-C5/C5’), 76.2 (CH-C2 or CH-1), 75.4 (CH₂-C11), 73.0 and 72.5 (CH-C4/C4’), 71.5 (CH₂-C11), 69.4 (CH-C10’), 67.6 (CH-C10), 67.1 and 67.0 (CH₂-C6/C6’), 41.0 and 40.0 (CH₂-C3/C3’), 33.4 (CH₂-C7’), 30.4 (CH₂-C7), 27.6 (6 x CH₃-tBu), 27.2 (6 x CH₃-tBu), 22.8 (2 x C-tBu), 20.1 (2 x C-tBu);

HRMS: (El’) for C₁₉H₃₄O₃Si ([M]⁺) calculated 370.2176, found 370.2177, Δ +0.5 ppm.
Dess-Martin periodinane (687 mg, 1.62 mmol) was added to a solution of alcohols 268 (300 mg, 0.810 mmol) in CH₂Cl₂ (30 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, then the reaction was quenched with a solution of saturated aqueous NaHCO₃ and Na₂S₂O₃ (1:1, 50 mL). The phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 50 mL). The organic extracts were combined, washed with brine (75 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 4:1) afforded the desired enone 228 (231 mg, 78% yield) as a colourless solid.

Rᵢ = 0.63 (petroleum ether—Et₂O, 1:1);
[α]₀ (25.3 °C, CHCl₃) = −97.8 (c = 1.10);
m.p. = 161–163 °C;
IR: νₘₐₓ 2957, 2933, 2860, 2364, 1672, 1666, 1473, 1095, 1036 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δ: 6.43 (1H, ddd, J = 12.4, 8.9, 7.6 Hz, CH–C₈), 5.86 (1H, d, J = 12.4 Hz, CH–C₉), 4.52 (1H, dd, J = 17.8, 0.9 Hz, CH₂–C₁₁), 4.20 (1H, d, J = 17.8 Hz, CH₂–C₁₁), 4.13 (1H, dd, J = 10.3, 5.0 Hz, CH₂–C₆), 3.81 (1H, ddd, J = 11.2, 9.2, 4.3 Hz, CH–C₄), 3.78 (1H, dd, J = 10.3, 10.3 Hz, CH₂–C₆), 3.43 (1H, ddd, J = 11.6, 9.1, 4.3 Hz, CH–C₂), 3.35–3.26 (2H, m, CH–C₁ and CH–C₅), 2.69–2.60 (1H, m, CH₂–C₇), 2.52 (1H, ddd, J = 15.0, 8.9, 0.9 Hz, CH₂–C₇), 2.43 (1H, ddd, J = 11.8, 4.3, 4.3 Hz, CH₂–C₃), 1.68 (1H, ddd, J = 11.8, 11.6, 11.2 Hz, CH₂–C₃), 1.04 (9H, s, CH₃–tBu), 0.99 (9H, s, CH₃–tBu);
¹³C NMR: (126 MHz, CDCl₃) δ: 203.6 (C–C₁₀), 137.7 (CH–C₈), 129.1 (CH–C₉), 84.8 (CH–C₂), 78.6 (CH₂–C₁₁), 77.7 (CH–C₅), 77.4 (CH–C₁), 72.7 (CH–C₄), 66.8 (CH₂–C₆), 39.6 (CH₂–C₃), 34.8 (CH₂–C₇), 27.5 (3 x CH₃–tBu), 27.2 (3 x CH₃–tBu), 22.7 (C–tBu), 20.1 (C–tBu);
HRMS: (EI⁺) for C₁₉H₃₂O₅Si ([M⁺]⁺) calculated 368.2019, found 368.2015, △ −1.2 ppm.
Allyl[(4aR,5aS,7Z,9E,11aR,12aS)-2,2-di-tert-butyl-4a,5a,6,11a,12,12a-hexahydro-4H-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-b]oxocin-9-yl] carbonate (283)

![Chemical Structure](image)

 Allylchloroformate (25 μL, 0.25 mmol) was added to a solution of enone 228 (78.0 mg, 0.210 mmol) in anhydrous THF (5 mL) at −78 ºC. The reaction mixture stirred for 10 min at −78 ºC, then NaHMDS (0.12 mL of a 2 M solution in THF, 0.25 mmol) was added dropwise. The solution was stirred for 2.5 h at −78 ºC, then the reaction was quenched with a 5% aqueous solution of KH₂PO₄ (10 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 19:1) afforded carbonate 283 (84.5 mg, 89% yield) as a colourless solid.

R_f = 0.81 (petroleum ether–Et₂O, 1:1);
[α]_D (29.3 ºC, CHCl₃) = +119.8 (c = 1.01);
m.p. = 111–113 ºC;

IR: ν_max 2934, 2861, 1759, 1651, 1474, 1366, 1244, 1221, 1094 cm⁻¹;

¹H NMR: (500 MHz, CDCl₃) δ_H 6.57 (1H, s, CH–C₁₁), 5.98–5.90 (2H, m, CH–C₁₄, CH–C₉), 5.71 (1H, ddd, J = 10.8, 8.6, 7.3 Hz, CH–C₈), 5.37 (1H, dddd, J = 17.2, 1.4, 1.4, 1.4 Hz, CH₂–C₁₅), 5.29 (1H, dddd, J = 10.4, 1.4, 1.4, 1.4 Hz, CH₂–C₁₅), 4.64 (2H, ddd, J = 5.8, 1.4, 1.2 Hz, CH₂–C₁₃), 4.40 (1H, ddd, J = 11.8, 9.1, 4.4 Hz, CH–C₂), 4.13 (1H, dd, J = 10.2, 4.9 Hz, CH₂–C₆), 3.77 (1H, dd, J = 10.2, 10.2 Hz, CH₂–C₆), 3.76–3.71 (1H, m, CH–C₄), 3.36–3.28 (2H, m, CH–C₁ and CH–C₅), 2.82 (1H, dddd, J = 14.1, 8.6, 3.8, 1.4 Hz, CH₂–C₇), 2.52 (1H, ddd, J = 14.1, 7.3, 2.8 Hz, CH₂–C₇), 2.43 (1H, ddd, J = 11.5, 4.4, 4.4 Hz, CH₂–C₃), 1.63 (1H, app q, J = 11.5 Hz, CH₂–C₃), 1.03 (9H, s, CH₃–tBu), 0.98 (9H, s, CH₃–tBu);
$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$ C 154.7 (C–C12), 141.6 (CH–C11), 131.3 (CH–C14), 129.9 (C–C10), 128.0 (CH–C8), 126.3 (CH–C9), 119.4 (CH$_2$–C15), 77.9 (CH–C5), 73.9 (CH–C1), 72.6 (CH–C4), 72.6 (CH–C2), 69.1 (CH$_2$–C13), 66.9 (CH–C6), 39.3 (CH$_2$–C3), 31.3 (CH$_2$–C7), 27.6 (3 x CH$_3$–tBu), 27.2 (3 x CH$_3$–tBu), 22.7 (C–tBu), 20.1 (C–tBu);

HRMS: (Cl, isobutane) for C$_{23}$H$_{37}$O$_7$Si ([M+H]$^+$) calculated 453.2309, found 453.2313, $\Delta +1.0$ ppm.


(S)-tBu-PHOX ligand (S)-282 (19.0 mg, 0.0480 mmol) was added to a suspension of tetrakis(triphenylphosphine)palladium (22.0 mg, 0.0200 mmol) in anhydrous THF (11 mL) at rt. After 30 min, a solution of carbonate 283 (84.5 mg, 0.190 mmol) in anhydrous THF (4 mL) was added and the reaction mixture stirred for 2.5 h at rt. The solution was filtered through a pad of Celite and the pad washed with Et$_2$O (3 x 25 mL). The resulting filtrate was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether–Et$_2$O, 19:1) to afford enone 227 as a colourless oil (66.3 mg, 85% yield, dr > 20:1).

$R_f = 0.78$ (petroleum ether–Et$_2$O, 1:1);

$[\alpha]_D$ (27.1 °C, CHCl$_3$) = $-124.0$ (c = 1.00);

IR: $\nu_{\text{max}}$ 2935, 2860, 1678, 1474, 1387, 1185, 1094 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$ H 6.41 (1H, ddd, $J = 12.3$, 9.8, 8.3 Hz, CH–C8), 5.88–5.78 (2H, m, CH–C9 and CH–C13), 5.20–5.14 (2H, m, CH$_2$–C14), 4.19 (1H, dd, $J = 9.2$, 3.6 Hz, CH–C11), 4.12 (1H, dd, $J = 10.1$, 4.9 Hz, CH$_2$–C6), 3.82–3.75 (2H, m, CH–C4 and CH$_2$–C6), 3.38 (1H, ddd, $J = 11.6$, 9.2, 4.1 Hz, CH–C2), 3.28 (1H,
ddd, \( J = 10.5, 9.7, 4.9 \) Hz, CH-C5), 3.26–3.21 (1H, m, CH-C1), 2.71–2.61 (2H, m, CH\(_2\)-C7 and CH\(_2\)-C12), 2.49–2.43 (2H, m, CH\(_2\)-C7 and CH\(_2\)-C3), 2.34–2.27 (1H, m, CH\(_2\)-C12), 1.64 (1H, app q, \( J = 11.6 \) Hz, CH\(_2\)-C3), 1.04 (9H, s, CH\(_3\)-tBu), 0.98 (9H, s, CH\(_3\)-tBu);

\(^{13}\text{C}\) NMR: (126 MHz, CDCl\(_3\)) \( \delta \) C 202.5 (C–C10), 136.4 (CH–C8), 134.0 (CH–C13), 130.7 (CH–C9), 118.5 (CH\(_2\)-C14), 88.2 (CH–C11), 85.6 (CH–C2), 77.9 (CH–C5), 77.8 (CH–C1), 72.8 (CH–C4), 66.8 (CH\(_2\)-C6), 40.5 (CH\(_2\)-C3), 37.1 (CH\(_2\)-C12), 33.9 (CH\(_2\)-C7), 27.5 (3 x CH\(_3\)-tBu), 27.1 (3 x CH\(_3\)-tBu), 22.7 (C-tBu), 20.0 (C-tBu);

HRMS: (ESI) for C\(_{22}\)H\(_{36}\)O\(_5\)SiNa ([M+Na]+) calculated 431.2230, found 431.2224, \( \Delta +4.3 \) ppm.


Methyl lithium (0.45 mL of a 1.4 m solution in Et\(_2\)O, 0.60 mmol) was added to a suspension of copper (I) cyanide (27.0 mg, 0.300 mmol) in anhydrous Et\(_2\)O (2.5 mL) at -78 °C. The reaction mixture was warmed to 0 °C, stirred until the solution turned colourless and then cooled back down to -78 °C. A solution of enone 227 (40.0 mg, 0.100 mmol) in anhydrous Et\(_2\)O (2.5 mL) was added and the reaction mixture stirred for 1.5 h at -78 °C. The reaction was quenched with a solution of saturated aqueous NH\(_4\)Cl and NH\(_4\)OH (5:1, 12 mL). The phases were separated and the aqueous phase extracted with Et\(_2\)O (3 x 15 mL). The organic extracts were combined, washed with brine (45 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et\(_2\)O, 19:1) afforded 225 (38 mg, 89% yield) as a colourless oil.

\( R_f = 0.85 \) (petroleum ether–Et\(_2\)O, 1:1);
\([\alpha]_D\) (28.0 °C, CHCl\(_3\)) = -122.0 (\( c = 1.00 \));
IR: $\nu_{\text{max}}$ 2934, 2860, 1715, 1457, 1094 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta_H$ 5.80 (1H, dddd, $J = 17.2, 10.2, 7.0, 7.0$ Hz, CH-C13), 5.14–5.08 (2H, m, CH$_2$-C14), 4.11 (1H, dd, $J = 10.1, 5.0$ Hz, CH$_2$-C6), 3.79–3.72 (2H, m, CH$_2$-C6 and CH-C4), 3.64 (1H, dd, $J = 9.2, 3.9$ Hz, CH-C11), 3.44 (1H, dd, $J = 10.9, 6.8$ Hz, CH$_2$-C9), 3.33 (1H, dd, $J = 8.9, 8.9$ Hz, CH-C1), 3.26 (1H, dddd, $J = 10.1, 10.1, 5.0$ Hz, CH-C5), 3.05 (1H, dddd, $J = 11.5, 8.9, 4.4$ Hz, CH-C2), 2.47 (1H, dddd, $J = 12.2, 4.4, 4.4$ Hz, CH$_2$-C3), 2.45–2.38 (1H, m, CH$_2$-C12), 2.30–2.22 (2H, m, CH$_2$-C12 and CH-C8), 1.84 (2H, m, CH$_2$-C9 and CH$_2$-C7), 1.64 (1H, dddd, $J = 12.2, 11.5, 11.3$ Hz, CH$_2$-C3), 1.33 (1H, dddd, $J = 15.2, 12.4, 8.9$ Hz, CH$_2$-C7), 1.04–0.97 (21H, m, CH$_3$-tBu and CH$_3$-C15);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta_C$ 216.1 (C-C10), 133.7 (CH-C13), 118.2 (CH$_2$-C14), 89.0 (CH-C11), 82.8 (CH-C2), 81.3 (CH-C5), 77.3 (CH-C1), 72.6 (CH-C4), 67.0 (CH$_2$-C6), 41.9 (CH$_2$-C7), 41.5 (CH$_2$-C9), 40.6 (CH$_2$-C3), 38.2 (CH$_2$-C12), 30.6 (CH-C8), 27.6 (3 x CH$_3$-tBu), 27.2 (3 x CH$_3$-tBu), 22.8 (C-tBu), 22.3 (C-tBu), 20.1 (CH$_3$-C15);

HRMS: (Cl, isobutane) for $C_{23}H_{41}O_5Si$ ([M+H]$^+$) calculated 425.2723, found 425.2719, $\Delta$ −0.9 ppm.
Pd/C (5%, 391 mg) was added to a solution of diol 233 (4.78 g, 36.7 mmol) in EtOAc (180 mL). The flask was flushed with H₂ three times before the reaction mixture was placed under an atmosphere of H₂ and stirred overnight at rt. The suspension was filtered through a pad of Celite and the pad washed with EtOAc (4 x 100 mL). The resulting filtrate was concentrated under reduced pressure to afford diol 292 (4.54 g, 94% yield) as a colourless oil.

\[ R_f = 0.28 \text{ (petroleum ether—Et}_2\text{O, 1:1);} \]
\[ [\alpha]_D (26.8 \degree C, \text{CHCl}_3) = +29.6 \text{ (c }= 1.11); \]
\[ \{\text{Lit.}^{159} [\alpha]_D (20 \degree C, \text{CH}_2\text{Cl}_2) = +33.3 \text{ (c }= 5.2)\}; \]
\[ \text{IR: } \nu_{\max} 3378, 2937, 2856, 1452, 1274, 1098, 1074, 1045, 1028 \text{ cm}^{-1}; \]
\[ ^1\text{H NMR:} (500 \text{ MHz, CDCl}_3) \delta_H 3.94–3.88 \text{ (1H, m, CH}_2\text{-C1), 3.79 (2H, dddd, J = 15.4, 13.8, 11.6, 4.3 Hz, CH}_2\text{-C6), 3.54 (1H, ddd, J = 10.5, 10.5, 4.7 Hz, CH-C4), 3.39–3.32 (1H, m, CH}_2\text{-C1), 3.11 (1H, ddd, J = 8.9, 4.7, 4.3 Hz, CH-C5), 3.00 (1H, br s, OH), 2.85 (1H, br s, OH), 2.13–2.07 (1H, m, CH}_2\text{-C3), 1.70–1.63 (2H, m, CH}_2\text{-C2), 1.47–1.37 (1H, m, CH}_2\text{-C3);} \]
\[ ^{13}\text{C NMR:} (126 \text{ MHz, CDCl}_3) \delta_C 81.9 (\text{CH-C5}), 67.8 (\text{CH}_2\text{-C1), 67.4 (CH-C4), 63.3 (CH}_2\text{-C6), 32.6 (CH}_2\text{-C3), 25.5 (CH}_2\text{-C2);} \]
\[ \text{HRMS: (Cl, isobutane) for C}_6\text{H}_{13}\text{O}_3 ([M+H]^{+}) \text{ calculated 133.0865, found 133.0875, } \Delta +4.6 \text{ ppm.} \]

\[
\text{C}_{18}H_{40}O_3Si_2 \\
\text{Molecular weight: 360.68 g mol}^{-1}
\]

TBSCl (14.4 g, 95.6 mmol), DMAP (773 mg, 6.33 mmol) and imidazole (8.68 g, 0.128 mol) were added to a solution of diol 292 (4.21 g, 31.9 mmol) in anhydrous DMF (110 mL) at 0 °C. The reaction mixture was stirred overnight at rt, cooled to 0 °C and then the reaction was quenched with H2O (100 mL). The phases were separated and the aqueous phase extracted with Et2O (4 x 125 mL). The organic extracts were combined, washed with brine (150 mL), dried (MgSO4) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et2O, 9:1) afforded 294 (10.7 g, 93% yield) as a colourless oil.

\[
\text{Rf} = 0.91 \text{ (petroleum ether–Et}_2\text{O, 1:1);} \\
[\alpha]_D (22.0 \degree \text{C, CHCl}_3) = +49.4 \ (c = 0.99); \\
\text{[Lit.}\] [\alpha]_D (20 \degree \text{C, CH}_2\text{Cl}_2) = +36.4 \ (c = 6.7)]; \\
\text{IR: } \nu_{max} 2928, 2857, 1471, 1462, 1362, 1252, 1099 \text{ cm}^{-1}; \\
^1\text{H NMR: (500 MHz, CDCl}_3 \text{)} \delta_H 3.92–3.88 \ (1\text{H, m, CH}_2\text{-C1}), 3.88 \ (1\text{H, dd, } J = 11.2, 1.9 \text{ Hz, CH}_2\text{-C6}), 3.67 \ (1\text{H, dd, } J = 11.2, 6.0 \text{ Hz, CH}_2\text{-C6}), 3.46 \ (1\text{H, ddd, } J = 10.6, 8.9, 4.8 \text{ Hz, CH-C4}), 3.31 \ (1\text{H, ddd, } J = 11.2, 4.8, 3.6 \text{ Hz, CH}_2\text{-C1}), 3.08 \ (1\text{H, ddd, } J = 8.9, 6.0, 1.9 \text{ Hz, CH-C5}), 2.03–1.96 \ (1\text{H, m, CH}_2\text{-C3}), 1.66–1.57 \ (2\text{H, m, CH}_2\text{-C2}), 1.47–1.38 \ (1\text{H, m, CH}_2\text{-C3}), 0.90 \ (9\text{H, s, CH}_3\text{-tBu}), 0.88 \ (9\text{H, s, CH}_3\text{-tBu}), 0.07 \ (3\text{H, s, CH}_3\text{-Me}), 0.06 \ (3\text{H, s, CH}_3\text{-Me}), 0.05 \ (6\text{H, s, CH}_3\text{-Me}); \\
^13\text{C NMR: (126 MHz, CDCl}_3 \text{)} \delta_C 83.9 \ (\text{CH-C5}), 67.6 \ (\text{CH-C4}), 67.4 \ (\text{CH}_2\text{-C1}), 63.9 \ (\text{CH}_2\text{-C6}), 33.7 \ (\text{CH}_2\text{-C3}), 26.2 \ (3 \times \text{CH}_3\text{-tBu}), 25.9 \ (3 \times \text{CH}_3\text{-tBu}), 25.7 \ (\text{CH}_2\text{-C2}), 18.7 \ (\text{C-tBu}), 18.1 \ (\text{C-tBu}), -4.0 \ (\text{CH}_3\text{-Me}), -4.7 \ (\text{CH}_3\text{-Me}), -4.8 \ (\text{CH}_3\text{-Me}), -5.0 \ (\text{CH}_3\text{-Me}); \\
\text{HRMS: (Cl, isobutane) for C}_{18}\text{H}_{41}O_3Si_2 \ ([M+H]^+) \text{ calculated 361.2594, found 361.2593, } \Delta \text{ -0.3 ppm.}
Camphorsulfonic acid (966 mg, 4.16 mmol) was added to a solution of 294 (5.00 g, 13.9 mmol) in CH₂Cl₂:MeOH (1:1, 160 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with Et₃N (0.95 mL, 6.7 mmol) and the mixture was concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—EtOAc, 2:1) afforded 295 (3.05 g, 89% yield) as a colourless oil.

Rf = 0.48 (petroleum ether—Et₂O, 1:1);  
[α]₀ (21.8 °C, CHCl₃) = +51.3 (c = 0.99);  
{Lit.} [α]₀ (21 °C, CHCl₃) = +50.3 (c = 1.01);  
IR: ν max 3485, 2930, 2857, 1462, 1362, 1094 cm⁻¹;  
¹H NMR: (500 MHz, CDCl₃) δH 3.94–3.89 (1H, m, CH₂-C1), 3.83 (1H, ddd, J = 11.3, 6.7, 3.1 Hz, CH₂-C6), 3.61 (1H, app dt, J = 11.3, 5.9 Hz, CH₂-C6), 3.48 (1H, ddd, J = 10.7, 9.0, 4.7 Hz, CH-C4), 3.37 (1H, ddd, J = 11.2, 7.9, 4.7 Hz, CH₂-C1), 3.14 (1H, ddd, J = 9.0, 5.9, 3.1 Hz, CH-C5), 2.05–2.00 (1H, m, CH₂-C3), 1.98 (1H, dd, J = 6.7, 5.9 Hz, OH), 1.70–1.61 (2H, m, CH₂-C2), 1.50–1.41 (1H, m, CH₂-C3), 0.88 (9H, s, CH₃-tBu), 0.07 (6H, s, CH₃-Me);  
¹³C NMR: (126 MHz, CDCl₃) δC 82.5 (CH-C5), 68.1 (CH-C4), 67.8 (CH₂-C1), 63.3 (CH₂-C6), 33.5 (CH₂-C3), 25.9 (3 x CH₃-tBu), 25.6 (CH₂-C2), 18.1 (C-tBu), −4.0 (CH₃-Me), −4.8 (CH₃-Me);  
HRMS: (Cl, isobutane) for C₁₂H₂₇O₃Si ([M+H]⁺) calculated 247.1729, found 247.1732, Δ +1.2 ppm.
(2S,3S)-3-((tert-Butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-carbaldehyde (296)$^{161}$

Et$_3$N (8.50 mL, 60.9 mmol) was added to a solution of 295 (3.00 g, 12.2 mmol) in anhydrous CH$_2$Cl$_2$ (45 mL) at 0 °C. A solution of sulfur trioxide pyridine complex (5.82 g, 36.5 mmol) in anhydrous DMSO (13 mL) was added dropwise and the reaction mixture stirred for 2 h at 0 °C. The resulting solution was diluted with H$_2$O (40 mL), the phases were separated and the aqueous phase extracted with CH$_2$Cl$_2$ (3 x 80 mL). The organic extracts were combined, washed with a saturated aqueous solution of CuSO$_4$ (100 mL) and brine (100 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (petroleum ether–Et$_2$O, 1:1) then used without further purification.
**tert-Butyldimethyl[(2R,3S)-2-vinyltetrahydro-2H-pyran-3-yl]oxy]silane (297)**

\[
\begin{array}{c}
\text{H} \\
\text{OTBS} \\
\text{C} \\
\text{H} \\
\text{O} \\
\text{3} \\
\text{4} \\
\text{5} \\
\text{6} \\
\text{7} \\
\text{H}
\end{array}
\]

\[
\text{C}_{13}\text{H}_{28}\text{O}_2\text{Si}
\]

**Molecular weight:** 242.43 g mol\(^{-1}\)

NaHMDS (24.4 mL of a 2 M solution in THF, 48.7 mmol) was added to a suspension of methyltriphenylphosphonium bromide (20.0 g, 56.1 mmol) in anhydrous THF (60 mL) at 0 °C. The reaction mixture was stirred for 45 min at 0 °C, then a solution of 296 [12.2 mmol] in anhydrous THF (135 mL) was added. The resulting mixture was stirred for 45 min at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH\(_4\)Cl (150 mL). The phases were separated and the aqueous phase extracted with Et\(_2\)O (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et\(_2\)O, 99:1) afforded 297 (2.23 g, 76% yield over two steps) as a colourless oil.

\(R_f = 0.85\) (petroleum ether–Et\(_2\)O, 1:1);

\([\alpha]_D\) (23.3 °C, CHCl\(_3\)) = +40.9 (c = 0.96);

{Lit.\(^{157}\)} [\(\alpha\)]\(_D\) (26 °C, CHCl\(_3\)) = +40.5 (c = 1.0));

**IR:** \(\nu_{\text{max}}\) 2930, 2857, 1471, 1362, 1254, 1125, 1094 cm\(^{-1}\);

\(^1\)H NMR: (500 MHz, CDCl\(_3\)) \(\delta_H\) 5.92 (1H, ddd, \(J = 17.2, 10.7, 5.8\) Hz, CH-C6), 5.31 (1H, ddd, \(J = 17.2, 1.8, 1.3\) Hz, CH\(_2\)-C7), 5.18 (1H, ddd, \(J = 10.7, 1.8, 1.3\) Hz, CH\(_2\)-C7), 3.96–3.91 (1H, m, CH\(_2\)-C1), 3.53–3.48 (1H, m, CH-C5), 3.38 (1H, ddd, \(J = 11.3, 11.3, 3.5\) Hz, CH\(_2\)-C1), 3.31 (1H, ddd, \(J = 10.5, 8.8, 4.6\) Hz, CH-C4), 2.07–1.99 (1H, m, CH\(_2\)-C3), 1.72–1.62 (2H, m, CH\(_2\)-C2), 1.49 (1H, ddd, \(J = 12.5, 10.5, 5.1\) Hz, CH\(_2\)-C3), 0.87 (9H, s, CH\(_3\)-tBu), 0.05 (3H, s, CH\(_3\)-Me), 0.03 (3H, s, CH\(_3\)-Me);

\(^{13}\)C NMR: (126 MHz, CDCl\(_3\)) \(\delta_C\) 137.1 (CH-C6), 116.6 (CH\(_2\)-C7), 83.4 (CH-C5), 71.5 CH-C4), 67.7 (CH\(_2\)-C1), 33.9 (CH\(_2\)-C3), 26.0 (3 x CH\(_3\)-tBu), 25.7 (CH\(_2\)-C2), 18.2 (C-tBu), −4.0 (CH\(_3\)-Me), −4.4 (CH\(_3\)-Me);

**HRMS:** (Cl, isobutane) for C\(_{13}\)H\(_{27}\)O\(_2\)Si ([M+H]\(^+\)) calculated 243.1780, found 243.1777, \(\Delta = 1.4\) ppm.
Camphorsulfonic acid (3.15 g, 13.6 mmol) was added to a solution of 297 (2.20 g, 9.08 mmol) in CH$_2$Cl$_2$:MeOH (1:1, 90 mL) at 0 °C. The resulting mixture was warmed to rt and stirred overnight. The reaction was quenched with Et$_3$N (2.25 mL, 16.3 mmol) and the resulting mixture was concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et$_2$O, 4:1 to 7:3) afforded alcohol 291 (1.12 g, 96% yield) as a colourless oil.

R$_f$ = 0.34 (petroleum ether—Et$_2$O, 1:1);
[$\alpha$]$_D$ (25.3 °C, CHCl$_3$) = +4.04 (c = 1.14);
{Lit.$^{163}$ [$\alpha$]$_D$ (25 °C, CHCl$_3$) = +6.5 (c = 1.2)};
IR: $\nu_{\text{max}}$ 3411, 2940, 2856, 1427, 1264, 1085, 1027 cm$^{-1}$;
$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$H 5.87 (1H, ddd, $J = 17.4$, 10.5, 7.1 Hz, CH-C6), 5.39 (1H, ddd, $J = 17.4$, 1.7, 1.1 Hz, CH$_2$-C7), 5.32 (1H, ddd, $J = 10.5$, 1.7, 0.8 Hz, CH$_2$-C7), 3.94 (1H, dddd, $J = 11.4$, 4.2, 2.0, 2.0 Hz, CH$_2$-C1), 3.50–3.46 (1H, m, CH-C5), 3.39 (1H, ddd, $J = 11.4$, 4.7, 3.6 Hz, CH$_2$-C1), 3.36–3.29 (1H, m, CH-C4), 2.19–2.12 (1H, m, CH$_2$-C3), 1.76–1.66 (3H, m, CH$_2$-C2 and OH), 1.49–1.40 (1H, m, CH$_2$-C3);
$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$C 136.3 (CH-C6), 119.1 (CH$_2$-C7), 84.2 (CH-C5), 69.7 (CH-C4), 67.6 (CH$_2$-C1), 31.7 (CH$_2$-C3), 25.5 (CH$_2$-C2);
HRMS: (Cl, isobutane) for C$_7$H$_{12}$O$_2$ ([M+H]$^+$) calculated 129.0916, found 129.0920, Δ +3.4 ppm.
A solution of alcohol 291 (500 mg, 3.90 mmol) in anhydrous THF (62 mL) was slowly added to a suspension of sodium hydride (374 mg of a 60% dispersion in mineral oil, 15.6 mmol) in anhydrous THF (62 mL) at 0 °C. The reaction mixture was warmed to rt, then triphenylchloroacetonylphosphorane (1.65 g, 4.68 mmol) and TBAI (74.0 mg, 0.200 mmol) were added. The resulting solution was heated to reflux and stirred for 3 h. The reaction mixture was cooled to rt and the reaction was quenched with H₂O (10 mL). The mixture was concentrated under reduced pressure and the aqueous phase was extracted with EtOAc (4 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude product 298 was used without any further purification.

Butyraldehyde (3.55 mL, 39.0 mmol) was added to a solution of crude phosphorane 298 [3.90 mmol] in anhydrous CH₂Cl₂ (145 mL). The reaction mixture was heated to reflux, stirred for 48 h then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 19:1 to 9:1) afforded the desired enone 299 (650 mg, 70% yield over two steps) as a colourless oil.

\[ R_f = 0.48 \text{ (petroleum ether–Et}_2\text{O, 1:1);} \]
\[ [\alpha]_D^{27.1 \circ} \text{ (CHCl}_3) = +35.1 \text{ (c = 1.09);} \]
\[ \text{IR: } \nu_{\text{max}} \text{ 2934, 2864, 1738, 1713, 1694, 1624, 1217, 1138, 1088 cm}^{-1}; \]
\[ ^1\text{H NMR: (500 MHz, CDCl}_3 \text{) } \delta_H 6.96 (1H, ddd, } J = 15.8, 6.9, 6.9 \text{ Hz, CH-C11), 6.30 (1H, ddd, } J = 15.8, 1.5, 1.5 \text{ Hz, CH-C10), 6.01 (1H, ddd, } J = 17.4, 10.7, 6.0 \text{ Hz, CH-C6), 5.39 (1H, ddd, } J = 17.4, 1.5, 1.5 \text{ Hz, CH}_2\text{-C7), 5.24 (1H, ddd, } J = 10.7, 1.5, 1.5 \text{ Hz, CH}_2\text{-C7), 4.25 (1H, d, } J = 16.5 \text{ Hz, CH}_2\text{-C8), 4.20 (1H, d, } J = 16.5 \text{ Hz, CH}_2\text{-C8), 3.96–3.92 (1H, m, CH}_2\text{-C1), 3.69–3.64 (1H, m, CH}_2\text{-C5), 3.40 (1H, ddd, } J = 11.5, 11.5, 2.7 \text{ Hz, CH}_2\text{-C1), 3.09 (1H, ddd, } J = 10.6, 8.9, 4.5 \text{ Hz, CH}_2\text{-C4),} \]
2.29–2.23 (1H, m, CH₂-C3), 2.20 (2H, dddd, J = 7.7, 7.4, 7.2, 1.5 Hz, CH₂-C12), 1.74–1.67 (1H, m, CH₂-C2), 1.68–1.59 (1H, m, CH₂-C2), 1.54–1.45 (3H, m, CH₂-C3 and CH₂-C13), 0.94 (3H, t, J = 7.4 Hz, CH₃-C14);

**¹³C NMR:** (126 MHz, CDCl₃) δC 197.3 (C-9), 148.4 (CH-C11), 136.7 (CH-C6), 126.2 (CH-C10), 117.3 (CH₂-C7), 81.4 (CH-C5), 79.2 (CH-C4), 74.0 (CH₂-C8), 67.5 (CH₂-C1), 34.8 (CH₂-C12), 29.6 (CH₂-C3), 25.3 (CH₂-C2), 21.4 (CH₂-C13), 13.9 (CH₃-C14);

**HRMS:** (Cl, isobutane) for C₁₄H₂₃O₃ ([M+H]⁺) calculated 239.1647, found 239.1645, Δ −0.9 ppm.

**\((E)-1\-\{(2R,3S)-2-Vinyl\text{-tetrahydro\-2H-pyran\-3-yl\}oxy\}\text{-hept-3-en-2-ol (300)}**

\[
\text{C₁₄H₂₄O₃} \\
\text{Molecular weight: 240.34 g.mol}^{-1}
\]

Cerium trichloride heptahydrate (484 mg, 1.30 mmol) and sodium borohydride (59.0 mg, 1.56 mmol) were added to a solution of enone 299 (309 mg, 1.30 mmol) in MeOH (70 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, then the reaction was quenched with a saturated aqueous solution of NH₄Cl (50 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure to afford an inseparable diastereomeric mixture of alcohols 300 (310 mg, 99% yield, dr 1:1) as a colourless oil

\(R_f = 0.39\) (petroleum ether–Et₂O; 1:1);

**IR:** \(ν_{\text{max}}\) 3453, 2956, 2929, 2861, 1464, 1269, 1216, 1110, 1088 cm\(^{-1}\);

\(^{1}H\ \text{NMR:** (500 MHz, CDCl}_3) \ δ_H 5.96 (2H, dddd, J = 17.3, 10.6, 6.5, 6.5 Hz, CH-C6/C6'), 5.75 (2H, app dtt, J = 15.0, 6.8, 1.2 Hz, CH-C11/C11'), 5.42–5.36 (2H, m, CH-C10/C10'), 5.37 (2H, d, J = 17.3 Hz, CH₂-C7/C7'), 5.25 (2H, dddd, J = 10.6, 5.0, 1.8, 1.1 Hz, CH₂-C7/C7'), 4.19 (2H, br s, CH-C5/C5'), 3.96–3.91 (2H, m, CH₂-C1/C1'), 3.63 (1H, dd, J = 9.4, 3.2 Hz, CH₂-C8), 3.61–3.57 (2H, m, CH-C4/C4'), 3.46–3.40 (2H, m, CH₂-C8'), 3.41–3.36 (2H, m, CH₂-C1/C1'), 3.19
(1H, dd, J = 9.4, 8.7 Hz, CH₂-C8), 3.10–3.04 (2H, m, CH-C9/C9’), 2.48 (1H, s, OH), 2.39 (1H, s, OH), 2.26–2.20 (2H, m, CH₂-C3/C3’), 2.01 (4H, dd, J = 14.5, 7.1 Hz, CH₂-C12/C12’), 1.75–1.59 (4H, m, CH₂-C2/C2’), 1.44–1.36 (6H, m, CH₂-C13/C13’ and CH₂-C3/C3’), 0.89 (6H, t, J = 7.4 Hz, CH₃-C14/C14’);

¹³C NMR: (126 MHz, CDCl₃) δC 136.9 and 136.8 (CH-C6/C6’), 134.1 and 134.0 (CH-C11/C11’), 128.2 and 128.0 (CH-C10/C10’), 117.7 and 117.5 (CH₂-C7/C7’), 81.6 and 81.5 (CH-C4/C4’), 78.7 and 78.2 (CH-C9/C9’), 73.9 (CH₂-C8), 73.4 (CH₂-C8’), 71.9 and 71.2 (CH-C5/C5’), 67.5 (CH₂-C1/C1’), 34.6 (CH₂-C12/C12’), 29.8 and 29.6 (CH₂-C3/C3’), 25.3 and 25.2 (CH₂-C2/C2’), 22.3 and 22.2 (CH₂-C13/C13’), 13.8 (CH₃-C14/C14’);

HRMS: (EI⁺) for C₁₄H₂₄O₃ ([M⁺]⁺) calculated 240.1725, found 240.1721, Δ −1.6 ppm.

(4aS,9aR)-3,4,4a,6,7,9a-Hexahydro-2H-pyrano[3,2-b]oxepin-7-ol (301)

Hoveyda-Grubbs second generation catalyst 150 (61.4 mg, 0.0980 mmol) was added to a solution of alcohols 300 (312 mg, 1.30 mmol) in degassed anhydrous CH₂Cl₂ (130 mL). The reaction mixture was heated to reflux and stirred overnight. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether–Et₂O, 1:1) to afford the desired alcohols 301 (178 mg, 81% yield, dr 1:1) as a separable mixture of diastereomers. (N.B. The two diastereomers were separated for characterisation but were usually taken on to the next step as a mixture.)

Diastereomer A

Rᶠ = 0.28 (petroleum ether–Et₂O, 1:1);
[α]₀ (27.2 °C, CHCl₃) = −20.9 (c = 1.04);
m.p. = 101–103 °C;
IR: νmax 3420, 2938, 2857, 2817, 1738, 1381, 1267, 1126, 1072 cm⁻¹;
**1H NMR:** (500 MHz, CDCl₃) δ H 5.73 (1H, ddd, J = 12.7, 3.9, 2.4 Hz, CH-C7), 5.55 (1H, ddd, J = 12.7, 2.2, 2.2 Hz, CH-C6), 4.45—4.40 (1H, m, CH-C8), 3.95 (1H, ddd, J = 11.5, 4.3, 1.4 Hz, CH₂-C9), 3.90—3.85 (1H, m, CH₂-C1), 3.75 (1H, ddd, J = 9.0, 4.6, 2.2 Hz, CH-C5), 3.38 (1H, dd, J = 11.5, 10.1 Hz, CH₂-C9), 3.26 (1H, m, CH₂-C1), 2.14 (1H, d, J = 5.7 Hz, OH), 2.08—2.02 (1H, m, CH₂-C3);

**13C NMR:** (126 MHz, CDCl₃) δ C 134.3 (CH-C7), 132.4 (CH-C6), 81.6 (CH-C5), 80.0 (CH-C4), 75.5 (CH₂-C9), 70.7 (CH-C8), 67.6 (CH₂-C1), 31.1 (CH₂-C3), 25.5 (CH₂-C2);

**HRMS:** (Cl, isobutane) for C₉H₁₃O₂ ([M-OH]⁺) calculated 153.0916, found 153.0912, Δ −2.5 ppm.

**Diastereomer B**

Rₚ = 0.13 (petroleum ether—Et₂O, 1:1);

[α]₀ (27.1 °C, CHCl₃) = −105.3 (c = 1.06);

**IR:** ν max 3426, 2944, 2861, 1740, 1370, 1216, 1148, 1096, 1059 cm⁻¹;

**1H NMR:** (500 MHz, CDCl₃) δ H 5.94 (1H, dddd, J = 12.4, 7.2, 2.8, 0.9 Hz, CH-C7), 5.69 (1H, dd, J = 12.4, 1.7 Hz, CH-C6), 4.12 (1H, ddd, J = 12.8, 3.0, 0.9 Hz, CH₂-C9), 3.98—3.94 (1H, m, CH-C5 and CH₂-C1), 3.70 (1H, dd, J = 12.8, 1.3 Hz, CH₂-C9), 3.35—3.29 (1H, m, CH-C4), 3.17 (1H, ddd, J = 10.8, 9.3, 4.6 Hz, CH₂-C1), 2.23 (1H, d, J = 8.5 Hz, OH), 2.16—2.08 (1H, m, CH₂-C3), 1.72—1.61 (2H, m, CH₂-C2), 1.59—1.47 (1H, m, CH₂-C3);

**13C NMR:** (126 MHz, CDCl₃) δ C 136.5 (CH-C6), 128.5 (CH-C7), 81.5 (CH-C5), 80.3 (CH-C4), 75.8 (CH₂-C9), 68.4 (CH-C8), 67.8 (CH₂-C1), 31.3 (CH₂-C3), 25.4 (CH₂-C2);

**HRMS:** (Cl, isobutane) for C₉H₁₃O₂ ([M-OH]⁺) calculated 153.0916, found 153.0920, Δ +3.1 ppm.
(4aS,9aR)-4,4a,6,9a-Tetrahydro-2H-pyrano[3,2-b]oxepin-7(3H)-one (289)

Dess-Martin periodinane (891 mg, 2.10 mmol) was added to a solution of alcohols 301 (178 mg, 1.05 mmol) in CH₂Cl₂ (40 mL) at 0 °C. The resulting mixture was warmed to rt and stirred overnight. The reaction was quenched with a solution of saturated aqueous Na₂S₂O₃ and NaHCO₃ (1:1, 50 mL). The phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 75 mL). The organic extracts were combined, washed with brine (125 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 4:1) afforded enone 289 (113 mg, 64% yield) as a colourless solid.

Rᵥ = 0.47 (petroleum ether–Et₂O, 1:1);
[α]ᵦ (28.9 °C, CHCl₃) = −54.8 (c = 1.06);
m.p. = 66–68 °C;
IR: νₑₜ₅ 2945, 2851, 2361, 2330, 1668, 1260, 1138, 1092 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δH 6.47 (1H, dd, J = 12.9, 2.5 Hz, CH-C7), 5.98 (1H, dd, J = 12.9, 2.5 Hz, CH-C6), 4.36 (1H, d, J = 18.3 Hz, CH₂-C9), 4.25 (1H, d, J = 18.3 Hz, CH₂-C9), 3.94 (1H, dddd, J = 6.0, 4.3, 4.2, 1.8 Hz, CH₂-C1), 3.86 (1H, ddd, J = 9.0, 2.5, 2.5 Hz, CH-C5), 3.44–3.39 (1H, m, CH₂-C1), 3.37 (1H, ddd, J = 11.0, 9.0, 4.8 Hz, CH-C4), 2.21–2.14 (1H, m, CH₂-C3), 1.75–1.68 (2H, m, CH₂-C2), 1.60–1.50 (1H, m, CH₂-C3);
¹³C NMR: (126 MHz, CDCl₃) δC 201.8 (C-C8), 146.3 (CH-C7), 127.8 (CH-C6), 81.1 (CH-C5), 79.8 (CH-C4), 77.4 (CH₂-C9), 68.3 (CH₂-C1), 30.7 (CH₂-C3), 25.5 (CH₂-C2);
HRMS: (Cl, isobutane) for C₉H₁₃O₃ ([M+H]+) calculated 169.0865, found 169.0861, Δ −2.4 ppm.
Allyl[(4aS,9aR)-3,4,4a,9a-tetrahydro-2H-pyrano[3,2-b]oxepin-7-yl]carbonate (302)

![Chemical Structure](image)

$\text{C}_{13}\text{H}_{16}\text{O}_5$

**Molecular weight:** 252.26 g.mol$^{-1}$

Allylchloroformate (0.12 mL, 1.1 mmol) was added to a solution of enone 289 (153 mg, 0.910 mmol) in anhydrous THF (15 mL) at −78 ºC. The reaction mixture was stirred for 10 min at −78 ºC, then NaHMDS (2.28 mL of a 1 M solution in THF, 2.28 mmol) was added. The reaction mixture was stirred for 2 h at −78 ºC, then the reaction was quenched with a 5% aqueous solution of KH$_2$PO$_4$ (20 mL). The phases were separated and the aqueous phase extracted with Et$_2$O (3 x 30 mL). The organic extracts were combined, washed with brine (75 mL), dried (MgSO$_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et$_2$O, 19:1) afforded carbonate 302 (173 mg, 76% yield) as a colourless oil.

$R_f = 0.83$ (petroleum ether–Et$_2$O, 1:1);

[$\alpha$]$\text{D}$ (24.7 ºC, CHCl$_3$) = +64.1 (c = 0.98);

**IR:** $\nu_{\text{max}}$ 2945, 2851, 1759, 1252, 1225, 1162, 1092 cm$^{-1}$;

**$^1\text{H NMR}$:** (500 MHz, CDCl$_3$) $\delta$H 6.72 (1H, s, CH-C9), 5.95 (1H, dddd, $J = 17.2, 10.4, 5.8, 5.8$ Hz, CH-C12), 5.79–5.69 (2H, m, CH-C7 and CH-C6), 5.39 (1H, dddd, $J = 17.2, 1.5, 1.4, 1.4$ Hz, CH$_2$-C13), 5.30 (1H, dddd, $J = 10.4, 1.5, 1.4, 1.4$ Hz, CH$_2$-C13), 4.66 (2H, ddd, $J = 5.8, 1.4, 1.4$ Hz, CH$_2$-C11), 3.95–3.90 (1H, m, CH$_2$-C1), 3.78–3.75 (1H, m, CH-C5), 3.52 (1H, ddd, $J = 11.3, 7.4, 5.0$ Hz, CH-C4), 3.38 (1H, ddd, $J = 11.4, 11.3, 3.1$ Hz, CH$_2$-C1), 2.39–2.31 (1H, m, CH$_2$-C3), 1.78–1.66 (2H, m, CH$_2$-C2), 1.64–1.55 (1H, m, CH$_2$-C3);

**$^{13}\text{C NMR}$:** (126 MHz, CDCl$_3$) $\delta$C 154.7 (C-C10), 142.5 (CH-C9), 133.8 (C-C8), 131.3 (CH-C12), 130.5 (CH-C7), 121.1 (CH-C6), 120.0 (CH$_2$-C13), 78.0 (CH-C5), 76.8 (CH-C4), 69.3 (CH$_2$-C11), 67.2 (CH$_2$-C1), 30.6 (CH$_2$-C3), 25.2 (CH$_2$-C2);

**HRMS:** (Cl, isobutane) for C$_{13}$H$_{17}$O$_5$ ([M+H]$^+$) calculated 253.1076, found 253.1073, Δ −1.4 ppm.
(4aS,6S,9aR)-6- Allyl-4,4a,6,9a-tetrahydro-2H-pyrano[3,2-b]oxepin-7(3H)-one (327)

(S)-tBu-PHOK ligand (S)-282 (66.0 mg, 0.170 mmol) was added to a suspension of tetrakis(triphenylphosphine)palladium (80.0 mg, 0.0690 mmol) in anhydrous THF (11 mL) at rt. The reaction mixture was stirred for 30 min and then a solution of carbonate 302 (173 mg, 0.690 mmol) in anhydrous THF (12 mL) was added. The reaction mixture was stirred for 2.5 h at rt, then concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (petroleum ether–Et2O, 19:1) to afford 327 (128 mg, 88% yield, dr 1:14) as a colourless solid.

Rf = 0.57 (petroleum ether–Et2O, 1:1);
[α]D (27.9 ºC, CHCl3) = −122.3 (c = 0.94);
m.p. = 47–49 ºC;
IR: νmax 2944, 2917, 2849, 1663, 1260, 1135, 1126, 1090, 1057 cm⁻¹;
1H NMR: (500 MHz, CDCl3) δH 6.46 (1H, dd, J = 12.6, 2.6 Hz, CH–C7), 6.00 (1H, dd, J = 12.6, 2.6 Hz, CH–C6), 5.87 (1H, dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, CH–C11), 5.16 (1H, dddd, J = 17.1, 1.6, 1.5, 1.5 Hz, CH2–C12), 5.13–5.09 (1H, m, CH2–C12), 4.26 (1H, dd, J = 10.0, 3.7 Hz, CH–C9), 3.96–3.91 (1H, m, CH2–C1), 3.88 (1H, ddd, J = 8.9, 2.6, 2.6 Hz, CH–C5), 3.51 (1H, ddd, J = 10.9, 8.9, 4.6 Hz, CH–C4), 3.43–3.37 (1H, m, CH2–C1), 2.74–2.68 (1H, m, CH2–C10), 2.53–2.45 (1H, m, CH2–C10), 2.14–2.08 (1H, m, CH2–C3), 1.75–1.66 (2H, m, CH2–C2), 1.61–1.52 (1H, m, CH2–C3);
13C NMR: (126 MHz, CDCl3) δC 202.4 (C–C8), 145.4 (CH–C7), 134.6 (CH–C11), 128.3 (CH–C6), 117.8 (CH2–C12), 83.2 (CH–C9), 80.5 (CH–C5), 73.5 (CH–C4), 68.2 (CH2–C1), 35.4 (CH2–C10), 30.6 (CH2–C3), 25.6 (CH2–C2);
HRMS: (EI⁺) for C12H16O3 ([M]+) calculated 208.1099, found 208.1100, Δ +0.2 ppm.
DBU (64 μL, 0.43 mmol) was added to a solution of 327 (88.8 mg, 0.430 mmol) in anhydrous toluene (5 mL). The reaction mixture was stirred for 48 h at rt, then the reaction was quenched with a saturated aqueous solution of NH₄Cl (7 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 10 mL). The organic extracts were combined, washed with brine (15 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude product was quickly filtered through a short pad of silica gel (petroleum ether—Et₂O, 1:1) to afford 288 (73.8 mg, 83% yield, dr 10:1) as a colourless oil.

R_f = 0.57 (petroleum ether—Et₂O, 1:1);
[α]_D (26.5 ° C, CHCl₃) = −8.30 (c = 1.00);
IR: ν_max 2944, 2925, 2852, 1664, 1261, 1127, 1092 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δ_H 6.41 (1H, dd, J = 12.8, 2.5 Hz, CH-C7), 5.95 (1H, dd, J = 12.8, 2.5 Hz, CH-C6), 5.82 (1H, dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.09 (1H, dddd, J = 17.1, 1.6, 1.5, 1.5 Hz, CH₂-C12), 5.06—5.03 (1H, m, CH₂-C12), 4.23 (1H, dd, J = 7.4, 4.2 Hz, CH-C9), 3.97—3.92 (1H, m, CH₂-C1), 3.83 (1H, ddd, J = 8.9, 2.5, 2.5 Hz, CH-C5), 3.42 (1H, ddd, J = 11.3, 11.3, 3.2 Hz, CH₂-C1), 3.34 (1H, ddd, J = 10.7, 8.9, 4.8 Hz, CH-C4), 2.59—2.53 (1H, m, CH₂-C10), 2.40 (1H, ddd, J = 14.7, 7.4, 6.9 Hz, CH₂-C10), 2.20—2.14 (1H, m, CH₂-C3), 1.74—1.66 (2H, m, CH₂-C2), 1.63—1.56 (1H, m, CH₂-C3);
¹³C NMR: (126 MHz, CDCl₃) δ_C 203.7 (C-C8), 144.8 (CH-C7), 133.7 (CH-C11), 128.0 (CH-C6), 117.7 (CH₂-C12), 86.8 (CH-C9), 80.6 (CH-C5), 78.6 (CH-C4), 68.3 (CH₂-C1), 37.9 (CH₂-C10), 30.6 (CH₂-C3), 25.5 (CH₂-C2);
HRMS: (EI') for C₁₂H₁₆O₃ ([M]+) calculated 208.1099, found 208.1103, Δ +1.9 ppm.
A solution of amine 309 (0.25 mL, 1.1 mmol) and Et$_3$N (0.17 mL, 1.3 mmol) in anhydrous toluene (2 mL) was added dropwise to a solution of phosphorus trichloride (97 μL, 1.1 mmol) in anhydrous toluene (15 mL) at rt. The reaction mixture was heated to 70 ºC and stirred for 6 h. The solution was cooled to rt and then Et$_3$N (0.28 mL, 2.05 mmol) was added. The reaction mixture was cooled to −78 ºC and (R)-BINOL (318 mg, 1.11 mmol) in anhydrous toluene:THF (4:1, 3.75 mL) was added dropwise. The solution was warmed slowly to rt then stirred overnight. The reaction mixture was filtered, then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–EtOAc, 19:1) afforded $R_a,S,S$-308 (275 mg, 46% yield) as a colourless solid.

$R_f = 0.31$ (petroleum ether–CH$_2$Cl$_2$, 3:1);

[$\alpha$]$_D$ (27.7 ºC, CHCl$_3$) = −449 (c = 0.94);

[{\textsuperscript{lit.}}$\alpha$]$_D$ (20 ºC, CHCl$_3$) = −456 (c = 0.79));

m.p. = 96–98 ºC

IR: $\nu_{max}$ 3059, 2973, 1591, 1463, 1376, 1327, 1231, 1204, 1071, 949 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$H 7.97–7.87 (4H, m, Ar), 7.62–7.07 (18H, m, Ar), 4.51 (2H, dq, $J = 13.9, 7.0$ Hz, 2 x CH), 1.73 (6H, d, $J = 7.0$ Hz, 2 x CH$_3$);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$C 150.3–121.1 (Ar), 52.48 (CH), 52.38 (CH), 21.6 (CH$_3$, taken from HSQC);

HRMS: (ESI) for C$_{36}$H$_{30}$NNaO$_2$P ([M+Na]$^+$) calculated 562.1912, found 562.1906, δ +4.5 ppm.
(4aS,6R,9S,9aR)-6-Allyl-9-methylhexahydro-2H-pyrano[3,2-b]oxepin-7(3H)-one (287)

\[ \text{C}_{13}\text{H}_{20}\text{O}_3 \]

Molecular weight: 224.30 g mol\(^{-1}\)

\(R_a,S,S\)-308 (6 mg, 0.01 mmol) was added to a solution of copper (II) triflate (2 mg, 0.005 mmol) in anhydrous toluene (0.75 mL) at rt. The reaction mixture was stirred at rt for 30 min, then cooled to \(-40\,^\circ\text{C}\). Dimethylzinc (0.2 mL of a 2 M solution in toluene, 0.4 mmol) was added dropwise, followed by a solution of \(288\) (18 mg, 0.087 mmol) in anhydrous toluene (0.75 mL). The solution was warmed to rt and allowed to stir overnight. The reaction was quenched with a saturated aqueous solution of \(\text{NH}_4\text{Cl}\). The phases were separated and the aqueous phase extracted with \(\text{Et}_2\text{O}\) (3 x 2 mL). The combined organic extracts were washed with brine (10 mL), dried (\(\text{MgSO}_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—\(\text{Et}_2\text{O}\), 19:1) afforded \(287\) (5.8 mg, 30\% yield) as a colourless oil.

\(R_f = 0.55\) (petroleum ether—\(\text{Et}_2\text{O}\), 1:1);

\(^1\text{H}\) NMR: (400 MHz, CDCl\(_3\)) \(\delta\) \(\text{H}\) 5.81 (1H, dddd, \(J = 17.1, 10.2, 6.9, 6.9\) Hz, CH-C11), 5.13–5.04 (2H, m, CH\(_2\)-C12), 3.94–3.88 (1H, m, CH\(_2\)-C7), 3.83 (1H, dd, \(J = 7.7, 5.1\) Hz, CH-C9), 3.30 (1H, ddd, \(J = 11.3, 11.3, 3.6\) Hz, CH\(_2\)-C7), 2.96 (1H, ddd, \(J = 10.4, 9.3, 4.7\) Hz, CH-C4), 2.88 (1H, dd, \(J = 12.0, 11.8\) Hz, CH\(_2\)-C1), 2.83 (1H, dd, \(J = 9.4, 9.3\) Hz, CH-C5), 2.43–2.30 (2H, m, CH\(_2\)-C10), 2.13 (1H, dd, \(J = 11.8, 1.9\) Hz, CH\(_2\)-C1), 2.10–2.06 (1H, m, CH\(_2\)-C3), 1.73–1.62 (3H, m, CH\(_2\)-C2 and CH-C6), 1.53–1.47 (1H, m, CH\(_2\)-C3), 1.12 (3H, d, \(J = 6.6\) Hz, CH\(_3\)-C13);

\(^{13}\text{C}\) NMR: (101 MHz, CDCl\(_3\)) \(\delta\) \(^{13}\text{C}\) 133.2 (CH-C11), 117.7 (CH\(_2\)-C12), 86.2 (CH-C5), 86.1 (CH-C9), 80.5 (CH-C4), 67.8 (CH\(_2\)-C7), 45.3 (CH\(_2\)-C1), 37.2 (CH\(_2\)-C10), 36.1 (CH-C6), 31.3 (CH\(_2\)-C3), 25.9 (CH\(_2\)-C2), 20.1 (CH\(_3\)-C13) (C-C8 not observed).
TBAF (9.15 mL of a 1.0 M solution in THF, 9.15 mmol) was added to a solution of 230 (1.00 g, 3.05 mmol) in anhydrous THF (50 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 48 h and then concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (CH₂Cl₂—MeOH, 19:1) to afford triol 314 which was used without further purification.

Imidazole (2.50 g, 36.6 mmol), TBSCl (4.60 g, 30.5 mmol) and DMAP (187 mg, 1.53 mmol) were added to a solution of 314 (1.03 g, 6.10 mmol) in anhydrous DMF (100 mL) at 0 °C. The reaction mixture was warmed to rt, stirred overnight and then the reaction was quenched with H₂O (100 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 125 mL). The organic extracts were combined, washed with brine (150 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 19:1) afforded 315 (2.85 g, 88% yield over two steps) as a colourless oil.
R_f = 0.91 (petroleum ether—Et_2O, 1:1);  
[α]_D (27.5 °C, CHCl_3) = −0.30 (c = 1.01);  
IR: ν_{max} 2928, 2857, 1472, 1462, 1362, 1252, 1080, 1005 cm^{-1};  
^1H NMR: (500 MHz, CDCl_3) δ_H 5.91 (1H, dddd, J = 17.1, 10.2, 7.0, 7.0 Hz, CH-C8),  
5.07 (1H, dddd, J = 17.1, 1.9, 1.5, 1.5 Hz, CH2-C9), 5.04–5.00 (1H, m, CH2-C9),  
3.81 (1H, dd, J = 11.4, 1.8 Hz, CH2-C6), 3.69 (1H, dd, J = 11.4, 4.8 Hz, CH2-C6),  
3.57 (1H, ddd, J = 11.3, 9.1, 4.7 Hz, CH-C4), 3.30 (1H, ddd, J = 11.0, 8.9,  
4.7 Hz, CH-C2), 3.09 (1H, ddd, J = 8.9, 8.6, 2.8 Hz, CH-C1), 3.04 (1H, ddd,  
J = 9.1, 4.8, 1.8 Hz, CH-C5), 2.55–2.48 (1H, m, CH2-C7), 2.20 (1H, ddd, J = 11.9,  
4.7, 4.7 Hz, CH2-C3), 2.10 (1H, ddd, J = 15.0, 8.6, 7.0 Hz, CH2-C7), 1.46 (1H,  
apq, J = 11.9, 11.3, 11.0 Hz, CH2-C3), 0.90–0.87 (27H, m, CH3-tBu), 0.07–0.04  
(18H, m, CH3-Me);  
^13C NMR: (126 MHz, CDCl_3) δ_C 135.7 (CH-C8), 116.4 (CH2-C9), 82.8 (CH-C5), 81.6  
(CH-C1), 69.9 (CH-C2), 65.9 (CH-C4), 62.9 (CH2-C6), 43.5 (CH2-C3), 36.3  
(CH2-C7), 26.1 (3 x CH3-tBu), 26.0 (3 x CH3-tBu), 25.9 (3 x CH3-tBu), 18.6  
(C-tBu), 18.1 (C-tBu), 18.1 (C-tBu), −3.8 (CH3-Me), −4.2 (CH3-Me), −4.5 (CH3-Me),  
−4.7 (CH3-Me), −4.9 (CH3-Me), −5.1 (CH3-Me);  
HRMS: (Cl, isobutane) for C_{27}H_{59}O_{4}Si_{3} ([M+H]^+) calculated 531.3721, found  
531.3728, Δ +1.3 ppm.

Camphorsulfonic acid (367 mg, 1.58 mmol) was added to a solution of 315 (2.79 g, 5.25 mmol) in CH₂Cl₂:MeOH (1:1, 200 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, then the reaction was quenched with Et₃N (0.40 mL, 2.6 mmol). The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et₂O, 9:1) to afford alcohol 316 (1.95 g, 89% yield) as a colourless oil.

Rₚ = 0.83 (petroleum ether—Et₂O, 1:1);
[α]₀ (25.9 °C, CHCl₃) = −0.50 (c = 1.01);
IR: νₘₐₓ 3497, 2955, 2930, 2886, 2859, 1471, 1252, 1078, 1005 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δₕ 5.87 (1H, dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, CH-C8), 5.11–5.02 (2H, m, CH₂-C9), 3.81 (1H, ddd, J = 10.6, 7.3, 3.1 Hz, CH₂-C6), 3.60–3.54 (1H, m, CH₂-C6), 3.51 (1H, ddd, J = 11.1, 9.0, 4.5 Hz, CH-C4), 3.34 (1H, ddd, J = 11.1, 9.0, 4.5 Hz, CH-C2), 3.20–3.13 (2H, m, CH-C1 and CH-C5), 2.59–2.53 (1H, m, CH₂-C7), 2.22 (1H, ddd, J = 12.0, 4.5, 4.5 Hz, CH₂-C3), 2.13–2.07 (1H, m, CH₂-C7), 1.98 (1H, dd, J = 7.3, 5.6 Hz, OH), 1.51 (1H, ddd, J = 12.0, 11.1, 11.1 Hz, CH₂-C3), 0.89 (9H, s, CH₃-tBu), 0.88 (9H, s, CH₃-tBu), 0.07 (6H, s, CH₃-Me), 0.06 (6H, s, CH₃-Me);
¹³C NMR: (126 MHz, CDCl₃) δ C 135.2 (CH-C8), 116.8 (CH₂-C9), 81.7 (CH-C5), 81.3 (CH-C1), 69.8 (CH-C2), 67.0 (CH-C4), 63.1 (CH₂-C6), 43.4 (CH₂-C3), 36.2 (CH₂-C7), 25.9 (3 x CH₃-tBu), 25.8 (3 x CH₃-tBu), 18.1 (C-tBu), 18.0 (C-tBu), −3.9 (CH₃-Me), −4.1 (CH₃-Me), −4.5 (CH₃-Me), −4.8 (CH₃-Me);
HRMS: (Cl, isobutane) for C₂₁H₄₅O₄Si₂ ([M+H]⁺) calculated 417.2856, found 417.2851, Δ −1.4 ppm.
(2S,3S,5R,6S)-6-Allyl-3,5-bis((tert-butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-carbaldehyde (317)

$$\text{C}_{21}\text{H}_{42}\text{O}_4\text{Si}_2$$

Molecular weight: 414.73 g/mol

Et$_3$N (3.14 mL, 22.6 mmol) was added to a solution of 316 (1.88 g, 4.51 mmol) in anhydrous CH$_2$Cl$_2$ (40 mL) at 0 °C. The reaction mixture was stirred for 5 min then sulfur trioxide pyridine complex (2.15 g, 13.5 mmol) in anhydrous DMSO (4.80 mL) was added dropwise. The solution was stirred for 3 h at 0 °C and then the reaction was quenched with H$_2$O (50 mL). The phases were separated and the aqueous phase extracted with CH$_2$Cl$_2$ (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (petroleum ether–Et$_2$O, 1:1) to afford aldehyde 317 that was used without further purification.

$\{[(2S,3R,5S,6R)-2-Allyl-6-vinyltetrahydro-2H-pyran-3,5-diyl]bis(oxy)]bistert-butyldimethylsilane (318)$

$$\text{C}_{22}\text{H}_{44}\text{O}_3\text{Si}_2$$

Molecular weight: 412.75 g/mol

NaHMDS (18.1 mL of a 1 M solution in THF, 18.1 mmol) was added to a suspension of methyltriphenylphosphonium bromide (7.40 g, 20.8 mmol) in anhydrous THF (30 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then a solution of crude 317 [4.51 mmol] in anhydrous THF (60 mL) was added. The reaction mixture was stirred for 1 h at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH$_4$Cl (100 mL). The phases were separated and the aqueous phase extracted with Et$_2$O (3 x 125 mL). The organic extracts were combined, washed with brine (150 mL), dried (MgSO$_4$) and concentrated
under reduced pressure. Flash column chromatography on silica gel (petroleum ether–EtO, 99:1) afforded diene 318 (1.69 g, 91% yield over two steps) as a colourless oil.

\[ R_f = 0.94 \text{ (petroleum ether–EtO, 1:1);} \]
\[ [\alpha]_D (26.6 \, ^\circ \text{C}, \text{CHCl}_3) = +1.14 \text{ (c = 1.10);} \]

**IR:** \( \nu_{\text{max}} 2954, 2930, 2885, 2858, 1642, 1473, 1362, 1251, 1082, 1005 \, \text{cm}^{-1} \);

**\(^1\text{H NMR}:** \( (500 \, \text{MHz, CDCl}_3) \delta \text{H} 5.97–5.86 \text{ (2H, m, CH-C9 and CH-6), 5.33 (1H, ddd, J = 17.4, 1.9, 1.6, CH}_2\text{-C7), 5.17 (1H, ddd, J = 10.7, 2.2, 1.6 Hz, CH}_2\text{-C7), 5.09 (1H, dddd, J = 17.2, 1.9, 1.5, 1.5 Hz, CH}_2\text{-C10), 5.06–5.03 (1H, m, CH}_2\text{-C10), 3.52 (1H, dd, J = 8.9, 5.4 Hz, CH-C5), 3.38 (1H, ddd, J = 11.0, 9.0, 4.5 Hz CH-C2), 3.34 (1H, ddd, J = 11.2, 8.9, 4.5 Hz, CH-C4), 3.16 (1H, ddd, J = 9.0, 8.5, 2.9 Hz, CH-C1), 2.59–2.52 (1H, m, CH}_2\text{-C8), 2.23 (1H, ddd, J = 12.0, 4.5, 4.5 Hz, CH}_2\text{-C3), 2.20–2.12 (1H, m, CH}_2\text{-C8), 1.52 (1H, ddd, J = 12.0, 11.2, 11.0 Hz, CH}_2\text{-C3), 0.89 (9H, s, CH}_3\text{-tBu), 0.87 (9H, s, CH}_3\text{-tBu), 0.07 (6H, s, CH}_3\text{-Me), 0.04 (6H, s, CH}_3\text{-Me);} \)

**\(^{13}\text{C NMR}:** \( (126 \, \text{MHz, CDCl}_3) \delta \text{C} 136.3 \text{ (CH-C9), 135.4 \text{ (CH-C6), 116.6 \text{ (CH}_2\text{-C7), 116.4 \text{ (CH}_2\text{-C10), 82.3 \text{ (CH-C5), 81.3 \text{ (CH-C1), 70.6 \text{ (CH-C4), 69.8 \text{ (CH-C2), 43.8 \text{ (CH}_2\text{-C3), 36.3 \text{ (CH}_2\text{-C8), 26.0 (3 x CH}_3\text{-tBu), 25.9 (3 x CH}_3\text{-tBu), 18.2 \text{ (C-tBu), 18.1 (C-tBu), } -3.8 \text{ (CH}_3\text{-Me), } -4.1 \text{ (CH}_3\text{-Me), } -4.4 \text{ (CH}_3\text{-Me), } -4.5 \text{ (CH}_3\text{-Me);} \)

**HRMS:** (Cl, isobutane) for \( \text{C}_{22}\text{H}_{45}\text{O}_3\text{Si}_2 \) \([\text{M+H}]^+ \) calculated 413.2907, found 413.2911, \( \Delta +1.0 \, \text{ppm} \).
Camphorsulfonic acid (2.18 g, 9.40 mmol) was added to a solution of 318 (1.55 g, 3.76 mmol) in CH$_2$Cl$_2$:MeOH (1:1, 60 mL) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with Et$_3$N (2.00 mL, 15.1 mmol) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–EtOAc, 3:7) afforded diol 313 (655 mg, 95% yield) as a colourless solid.

$R_f = 0.13$ (petroleum ether–Et$_2$O, 1:1);
$[\alpha]_D$ (22.2 °C, CHCl$_3$) = +2.20 (c = 1.00);

m.p. = 39–41 °C;

IR: $\nu_{\max}$ 3356, 2924, 2859, 1641, 1431, 1354, 1080, 1030 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$H 5.95 (1H, dddd, J = 17.2, 10.2, 7.0, 7.0 Hz, CH–C9), 5.85 (1H, ddd, J = 17.4, 10.5, 6.9 Hz, CH–C6), 5.41 (1H, ddd, J = 17.4, 1.6, 1.1 Hz, CH$_2$–C7), 5.33 (1H, ddd, J = 10.5, 1.6, 0.9 Hz, CH$_2$–C7), 5.15 (1H, dddd, J = 17.2, 1.9, 1.9, 1.5 Hz, CH$_2$–C10), 5.09 (1H, ddd, J = 10.2, 1.9, 1.0 Hz, CH$_2$–C10), 3.56–3.46 (2H, m, CH–C5 and CH–C2), 3.41–3.34 (1H, m, CH–C4), 3.20 (1H, ddd, J = 9.1, 6.9, 4.3 Hz, CH–C1), 2.61–2.52 (1H, m, CH$_2$–C8), 2.46 (1H, ddd, J = 11.6, 4.6, 4.6 Hz, CH$_2$–C3), 2.40–2.30 (1H, m, CH$_2$–C8), 1.71 (1H, d, J = 3.5 Hz, OH), 1.65 (1H, d, J = 5.2 Hz, OH), 1.49 (1H, app q, J = 11.6 Hz, CH$_2$–C3);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$C 135.7 (CH–C6), 134.9 (CH–C9), 119.3 (CH$_2$–C7), 117.3 (CH$_2$–C10), 83.5 (CH–C5), 80.9 (CH–C1), 69.4 (CH–C2), 68.8 (CH–C4), 40.9 (CH$_2$–C3), 36.8 (CH$_2$–C8);

HRMS: (CI, isobutane) for C$_{10}$H$_{17}$O$_3$ ([M+H]$^+$) calculated 185.1178, found 185.1174, Δ = −2.2 ppm.
A 30% aqueous solution of NaOH (6 mL) was added to a solution of 313 (176 mg, 0.960 mmol) in toluene (6 mL) at 0 °C. After 5 min, tert-butyl-bromoacetate (0.60 mL, 3.8 mmol) and TBAI (355 mg, 0.960 mmol) were added and the reaction mixture was stirred overnight at rt. A further 1 eq of TBAI (355 mg, 0.960 mmol) and 3 eq of tert-butyl-bromoacetate (0.60 mL, 3.8 mmol) were added and the reaction mixture was stirred overnight. The solution was diluted with toluene (10 mL) and H$_2$O (10 mL). The phases were separated and the aqueous phase extracted with toluene (3 x 15 mL). The organic extracts were combined, washed with 1 M HCl (30 mL) and brine (30 mL), dried (MgSO$_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et$_2$O, 19:1) afforded ester 319 (210 mg, 53% yield) as a colourless oil.

R$_f$ = 0.63 (petroleum ether–Et$_2$O, 1:1);
[α]$_D$ (26.8 °C, CHCl$_3$) = −8.78 (c = 0.95);
IR: $\nu_{max}$ 2980, 2931, 1749, 1730, 1369, 1303, 1252, 1226, 1126 cm$^{-1}$;
$^1$H NMR: (500 MHz, CDCl$_3$) $\delta$H 6.00 (1H, ddd, $J$ = 17.1, 10.7, 5.5 Hz, CH–C6), 5.97–5.88 (1H, m, CH–C9), 5.41 (1H, ddd, $J$ = 17.1, 1.5, 1.5 Hz, CH$_2$–C7), 5.23 (1H, ddd, $J$ = 10.7, 1.5, 1.5 Hz, CH$_2$–C7), 5.11 (1H, dd, $J$ = 17.2, 1.9, 1.5, 1.5 Hz, CH$_2$–C10), 5.07–5.02 (1H, m, CH$_2$–C10), 4.06–3.96 (4H, m, CH$_2$–C11 and CH$_2$–C11'), 3.64 (1H, dd, $J$ = 9.3, 5.6 Hz, CH–C4), 3.30 (1H, ddd, $J$ = 9.7, 7.6, 3.2, CH–C1), 3.18 (1H, ddd, $J$ = 12.0, 9.7, 5.0 Hz, CH–C2), 3.13 (1H, ddd, $J$ = 11.2, 9.3, 4.6 Hz, CH–C5), 2.73 (1H, ddd, $J$ = 12.0, 5.0, 4.7 Hz, CH$_2$–C3), 2.70–2.65 (1H, m, CH$_2$–C8), 2.28 (1H, ddd, $J$ = 14.8, 7.6, 7.6 Hz, CH$_2$–C8), 1.48 (9H, s, CH$_3$–C14) 1.47 (9H, s, CH$_3$–C14'), 1.51–1.44 (1H, m, CH$_2$–C3);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$C 169.7 and 169.5 (C–C12/C12'), 135.8 (CH–C6), 135.1 (CH–C9), 117.3 (CH$_2$–C7), 116.9 (CH$_2$–C10), 81.8 and 81.7 (C–C13/C13'),
80.7 (CH-C4), 79.6 (CH-C1), 78.1 (CH-C2), 77.0 (CH-C5), 67.9 and 67.1 (CH2-C11/C11′), 36.3 (CH2-C8), 35.6 (CH2-C3), 28.3 (3 x CH3-C14 and 3 x CH3-C14′).

(3E,3′E)-1,1′-[[2S,3R,5S,6R]-2-Allyl-6-vinyltetrahydro-2H-pyran-3,5-diyl]bis(oxy)]bis(hept-3-en-2-one) (312)

A solution of 313 (300 mg, 1.63 mmol) in anhydrous THF (30 mL) was added to a suspension of sodium hydride (313 mg of a 60% suspension in mineral oil, 13.1 mmol) in anhydrous THF (30 mL) at 0 °C. The reaction mixture was warmed to rt, then triphenylchloroacetonylphosphorane (1.38 g, 3.91 mmol) and TBAI (60.0 mg, 0.160 mmol) were added. The reaction mixture was heated to reflux, stirred for 3 h then cooled to rt and the reaction was quenched with H2O (15 mL). The solution was concentrated under reduced pressure and the aqueous phase extracted with EtOAc (4 x 75 mL). The organic extracts were combined, washed with brine (125 mL), dried (MgSO4) and concentrated under reduced pressure. The crude phosphorane 322 was then used without further purification.

Butyraldehyde (4.40 mL, 48.9 mmol) was added to a solution of crude 322 [1.63 mmol] in anhydrous CH2Cl2 (60 mL). The reaction mixture was heated to reflux and stirred for 48 h. The solution was concentrated under reduced pressure and the crude residue product purified by flash column chromatography on silica gel (petroleum ether–Et2O, 8:2) to afford enone 312 (570 mg, 86% yield over two steps) as a pale yellow oil.
$R_f = 0.65$ (petroleum ether–$\text{Et}_2\text{O}$, 1:1);
$[\alpha]_D$ (23.4 $^\circ$C, CHCl$_3$) = +1.55 (c = 0.97);

IR: $\nu_{\text{max}}$ 2959, 2932, 2905, 2872, 1694, 1624, 1456, 1433, 1339, 1290, 1085 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta_H$ 6.95 (2H, dddd, $J = 15.9, 9.1, 6.9, 6.9$ Hz, CH-C14/C14'), 6.26 (2H, dddd, $J = 15.9, 5.7, 1.5, 1.5$ Hz, CH-C13/C13'), 6.00–5.89 (2H, m, CH-C6 and CH-C9), 5.41 (1H, ddd, $J = 17.2, 1.9, 1.6$ Hz, CH$_2$-C7), 5.24 (1H, ddd, $J = 10.7, 1.9, 1.6$ Hz, CH$_2$-C7), 5.09 (1H, ddd, $J = 17.3, 3.3, 1.4$ Hz, CH$_2$-C10), 5.07–5.03 (1H, m, CH$_2$-C10), 4.30 (1H, d, $J = 16.4$ Hz, CH$_2$-C11), 4.26 (1H, d, $J = 16.6$ Hz, CH$_2$-C11'), 4.22 (1H, d, $J = 16.6$ Hz, CH$_2$-C11'), 4.19 (1H, d, $J = 16.4$ Hz, CH$_2$-C11), 3.69 (1H, dd, $J = 9.2, 5.7$ Hz, CH-C5), 3.36 (1H, ddd, $J = 9.2, 7.4, 3.3$ Hz, CH-C1), 3.16 (1H, ddd, $J = 11.1, 9.2, 4.5$ Hz, CH-C2), 3.09 (1H, ddd, $J = 11.2, 9.2, 4.5$ Hz, CH-C4), 2.71 (1H, ddd, $J = 11.8, 4.5, 4.5$ Hz, CH$_2$-C3), 2.67–2.61 (1H, m, CH$_2$-C8), 2.29 (1H, ddd, $J = 14.6, 7.4, 7.3$ Hz, CH$_2$-C8), 2.20 (4H, 2 x app p, $J = 7.3$ Hz and $J = 7.3$ Hz, CH$_2$-C15/C15'), 1.54–1.46 (5H, m, CH$_2$-C16/C16' and CH$_2$-C3), 0.94 (6H, 2 x t, $J = 7.4$ Hz and $J = 7.4$ Hz, CH$_3$-C17/C17');

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta_C$ 196.8 and 196.5 (C-C12/C12'), 149.0 (CH-C14/C14'), 135.8 (CH-C6), 134.8 (CH-C9), 126.2 and 126.1 (CH-C13/C13'), 117.5 (CH$_2$-C7), 117.0 (CH$_2$-C10), 80.7 (CH$_2$-C5), 79.4 (CH-C1), 78.2 (CH-C4), 76.9 (CH-C2), 74.1 and 73.4 (CH$_2$-C11/C11'), 36.3 (CH$_2$-C8), 35.3 (CH$_2$-C3), 34.8 (CH$_2$-C15/C15'), 21.4 (CH$_2$-C16/C16'), 13.8 (CH$_3$-C17/C17');

HRMS: (EI') for C$_{24}$H$_{36}$O$_5$ ([M]$^+$) calculated 404.2563, found 404.2566, $\Delta$ +0.7 ppm.
(3E,3'E)-1,1'{-[[(2S,3R,5S,6R)-2-Allyl-6-vinyltetrahydro-2H-pyran-3,5-diyl]bis(oxy)]bis(hept-3-en-2-ol)} (323)

Cerium trichloride heptahydrate (428 mg, 1.15 mmol) and sodium borohydride (44.0 mg, 1.15 mmol) were added to a solution of 312 (200 mg, 0.480 mmol) in MeOH (25 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C and then the reaction was quenched with a saturated aqueous solution of NH₄Cl (35 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure to afford alcohols 323 (188 mg, 96% yield, dr 1:1) as a colourless oil. Alcohols 323 were used in the next step without further purification.

Rₛ = 0.39 (petroleum ether−Et₂O, 1:1)
IR: νₘₐₓ 3430, 2957, 2926, 2870, 1458, 1344, 1288, 1107, 970 cm⁻¹.
HRMS: (Cl, isobutane) for C₂₄H₄₁O₅ ([M+H]⁺) calculated 409.2954, found 409.2955, Δ +0.2 ppm.
Hoveyda-Grubbs second generation catalyst 150 (12.0 mg, 0.0190 mmol) was added to a solution of 323 (76.0 mg, 0.190 mmol) in degassed anhydrous CH₂Cl₂ (20 mL). The reaction mixture was heated to reflux and stirred overnight. The solution was concentrated under reduced pressure and the crude product used without further purification.

\[ R_f = 0.10 \text{ (petroleum ether--Et}_2\text{O, 1:1)} \]

Dess-Martin periodinane (161 mg, 0.380 mmol) was added to a solution of crude 324 [0.190 mmol] in CH₂Cl₂ (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then the reaction was quenched with a solution of saturated aqueous Na₂S₂O₃ and NaHCO₃ (1:1, 20 mL). The phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 25 mL). The organic extracts were combined, washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 1:1) afforded enone 311 (19.7 mg, 39% yield over two steps) as a colourless solid.
R_f = 0.21 (petroleum ether–Et_2O, 1:1);
[α]_D (25.6 °C, CHCl_3) = −87.3 (c = 1.00);

m.p. = 175–177 ºC;

IR: ν_{max} 2959, 2922, 2872, 2356, 1684, 1669, 1465, 1281, 1120, 1077, 1014 cm^{-1};

^1H NMR: (500 MHz, CDCl_3) δ_H 6.50 (1H, dd, J = 12.9, 2.0 Hz, CH-C6), 6.46 (1H, ddd, J = 12.3, 9.0, 8.0 Hz, CH-C11), 6.03 (1H, dd, J = 12.9, 2.6 Hz, CH-C7), 5.89 (1H, d, J = 12.3 Hz, CH-C12), 4.53 (1H, dd, J = 17.7, 0.9 Hz, CH_2-C14), 4.39 (1H, d, J = 18.2 Hz, CH_2-C9), 4.26 (1H, d, J = 18.2 Hz, CH_2-C9), 4.22 (1H, d, J = 17.7 Hz, CH_2-C14), 3.97 (1H, ddd, J = 9.0, 2.6, 2.0 Hz, CH-C5), 3.49 (1H, ddd, J = 11.2, 9.0, 4.8 Hz, CH-C4), 3.43 (1H, ddd, J = 11.6, 9.2, 4.1 Hz, CH-C2), 3.36 (1H, ddd, J = 9.2, 9.0, 1.3 Hz, CH-C1), 2.73–2.65 (1H, m, CH_2-C10), 2.60 (1H, ddd, J = 14.8, 9.0, 1.1 Hz, CH_2-C10), 2.48 (1H, ddd, J = 12.2, 4.8, 4.1 Hz, CH_2-C3), 1.80 (1H, ddd, J = 12.2, 11.6, 11.2 Hz, CH_2-C3);

^13C NMR: (126 MHz, CDCl_3) δ_C 203.2 (C-C8), 201.2 (C-C13), 144.6 (CH-C6), 137.2 (CH-C11), 129.5 (CH-C12), 128.4 (CH-C7), 84.6 (CH-C2), 80.8 (CH-C5), 79.0 (CH_2-C14), 78.7 (CH-C4), 77.8 (CH-C1), 77.5 (CH_2-C9), 37.6 (CH_2-C3), 34.6 (CH_2-C10).

Diallyl[(5aR,6aS,8Z,10E,12aR,13aS)-5a,6a,7,12a,13,13a-hexahydrooxepino[2′,3′:5,6]pyrano[3,2-b]oxocine-3,10-diyl]dicarbonate (325)

![Chemical Structure](image)

C_{22}H_{24}O_{9}

Molecular weight: 423.42 g.mol^{-1}

Allylchloroformate (0.05 mL, 0.4 mmol) was added to a solution of 311 (47.9 g, 0.180 mmol) in anhydrous THF (3 mL) at −78 ºC. The reaction mixture was stirred for 10 min, then NaHMDS (0.90 mL of a 1 M solution in THF, 0.90 mmol) was added. The reaction mixture was stirred for 3 h at −78 ºC, then the reaction was quenched with a 5% solution of KH_2PO_4 (5 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (15 mL), dried (MgSO_4) and concentrated
under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et$_2$O, 9:1) afforded carbonate 325 (53.5 g, 69% yield) as an unstable colourless solid.

$R_f = 0.74$ (petroleum ether–Et$_2$O, 1:1);
IR: $\nu_{\text{max}}$ 2949, 2360, 1758, 1246, 1221, 1160, 1053, 1032 cm$^{-1}$;
$^1$H NMR: (500 MHz, CDCl$_3$) $\delta_H$ 6.68 (1H, s, CH-C9 or CH-C14), 6.56 (1H, s, CH-9 or CH-14), 5.99–5.87 (4H, m, CH-C17/C17' and CH-C7 and CH-C12), 5.78–5.70 (2H, m, CH-C11 and CH-C6), 5.39 (1H, dddd, $J = 6.8, 1.5, 1.3, 1.3$ Hz, CH$_2$-C18 or C18'), 5.35 (1H, dddd, $J = 6.8, 1.5, 1.3, 1.3$ Hz, CH$_2$-C18 or 18'), 5.32–5.26 (2H, m, CH$_2$-C18/C18'), 4.65 (2H, d, $J = 5.8$ Hz, CH$_2$-C16 or C16'), 4.63 (2H, d, $J = 5.8$ Hz, CH$_2$-C16 or C16'), 4.47–4.38 (1H, m, CH-C2), 3.87 (1H, d, $J = 7.4$ Hz, CH-C5), 3.67–3.60 (1H, m, CH-C4), 3.33 (1H, dddd, $J = 8.8, 3.2, 3.2$ Hz, CH=C1), 2.90–2.82 (1H, m, CH$_2$-C10), 2.62–2.54 (2H, m, CH$_2$-C10 and CH$_2$-C3), 1.79 (1H, app q, $J = 11.8$ Hz, CH$_2$-C3).

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta_C$ 154.7 and 154.6 (C-C15/C15'), 142.1 (CH-C9 or CH-C14), 141.3 (CH-C9 or CH-C14), 133.5 (CH-C12 or CH-C7), 133.0 (C-C8 or C-C13), 131.3 and 131.2 (CH$_2$-C17/C17'), 130.0 (C-C8 or C-C13), 129.5 (CH-C11 or CH-C6), 128.1 (CH-C12 or CH-C7), 121.3 (CH-C11 or CH-C6), 119.6 and 119.4 (CH$_2$-C18/C18'), 77.9 (CH-C5), 76.3 (CH-C4), 72.7 (CH-C1), 72.3 (CH=C2), 69.3 and 69.1 (CH$_2$-C16/C16'), 36.9 (CH$_2$-C3), 31.3 (CH$_2$-C10);

HRMS: (EI') for C$_{22}$H$_{24}$O$_9$ ([M]$^+$) calculated 432.1420, found 432.1419, $\Delta$ –0.4 ppm.
(5aR,6aS,12aR,13aS,Z)-2,11-Diallyl-6a,7,11,12a,13,13α-hexahydrooxepino[2',3':5,6]pyrano[3,2-b]oxocine-3,10(2H,5αH)-dione (328)

(S)-tBu-PHOX ligand (S)-282 (19.4 mg, 0.0500 mmol) was added to a solution of tetrakis(triphenylphosphine)palladium (23.0 mg, 0.0200 mmol) in degassed anhydrous THF (5.5 mL) at rt. The reaction mixture was stirred for 30 min at rt, then a solution of 325 (43.9 g, 0.100 mmol) in degassed anhydrous THF (2.5 mL) was added. The reaction was stirred for 2.5 h at rt, then concentrated under reduced pressure. The crude product was filtered through a small pad of silica (petroleum ether–Et₂O, 3:1) to afford enone 328 (29.0 mg, 84% yield) as a mixture of diastereomers. (Mixture of diastereomers identified by crude 1H NMR analysis.)

R_f = 0.36 (petroleum ether–Et₂O, 1:1);
IR: ν_max 2917, 2873, 1674, 1660, 1297, 1275, 1103, 1075, 1020 cm⁻¹;
HRMS: (EI⁺) for C_{20}H_{24}O_{5} ([M⁺]⁺) calculated 344.1624, found 344.1620, Δ -1.2 ppm.

DBU (12.5 μL, 0.0840 mmol) was added to a solution of 328 (29.0 mg, 0.084 mmol) in anhydrous toluene (1.5 mL) at rt. The reaction mixture was stirred at rt in the dark for 24 h. The reaction was quenched with a saturated aqueous solution of NH₄Cl (2 mL), then the phases were separated and the aqueous phase extracted with Et₂O (3 x 5 mL). The organic extracts were
combined, washed with brine (7.5 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. A quick filtration through a small pad of silica gel (petroleum ether—Et\(_2\)O, 1:1) afforded the desired enone 310 (8.9 mg, 31% yield, dr 6:1) as a colourless oil.

\(R_f = 0.37\) (petroleum ether—Et\(_2\)O, 1:1);

\([\alpha]_D^\circ\) (25.4 °C, CHCl\(_3\)) = −87.6 (c = 0.28);

IR: \(\nu_{\text{max}}\) 2926, 2864, 2357, 2341, 1669, 1660, 1107, 1087, 1058, 1034, 1016 cm\(^{-1}\);

\(^1\)H NMR: (500 MHz, CDCl\(_3\)) \(\delta\) 6.47–6.40 (2H, m, CH-14 and CH-6), 5.98 (1H, dd, \(J = 12.8, 2.6\) Hz, CH-C7), 5.91 (1H, d, \(J = 12.3\) Hz, CH-C15), 5.87–5.78 (2H, m, CH-C19 and CH-C11), 5.20–5.05 (4H, m, CH\(_2\)-C20 and CH\(_2\)-C12), 4.25 (1H, dd, \(J = 7.4, 4.3\) Hz, CH-C9), 4.19 (1H, dd, \(J = 9.2, 3.6\) Hz, CH-C17), 3.92 (1H, ddd, \(J = 9.0, 2.4, 2.4\) Hz, CH-C5), 3.44 (1H, ddd, \(J = 11.3, 9.0, 4.8\) Hz, CH-C4), 3.39–3.34 (1H, m, CH-C2), 3.28 (1H, ddd, \(J = 10.1, 9.5, 1.1\) Hz, CH-C1), 2.75–2.69 (1H, m, CH\(_2\)-C13), 2.68–2.62 (1H, m, CH\(_2\)-C18), 2.59–2.53 (2H, m, CH\(_2\)-C13 and CH\(_2\)-C3), 2.50–2.45 (1H, m, CH\(_2\)-C10), 2.45–2.38 (1H, m, CH\(_2\)-C10), 2.34–2.27 (1H, m, CH\(_2\)-C18), 1.77 (1H, ddd, \(J = 12.2, 11.6, 11.3\) Hz, CH\(_2\)-C3);

\(^{13}\)C NMR: (126 MHz, CDCl\(_3\)) \(\delta\) C 203.2 and 202.3 (C-16 and C-8), 143.2 (CH-C15), 136.2 (CH-C7), 134.0 and 133.4 (CH-C19 and CH-C11), 130.9 (CH-C6), 128.5 (CH-C14), 118.7 and 118.0 (CH\(_2\)-C20 and CH\(_2\)-C12), 88.2 (CH-C17), 86.9 (CH-C9), 85.2 (CH-C2), 80.4 (CH-C5), 77.9 (CH-C1), 77.5 (CH-C4), 38.2 (CH\(_2\)-C10), 37.9 (CH\(_2\)-C3), 37.1 (CH\(_2\)-C18), 33.9 (CH\(_2\)-C13);

HRMS: (ESI) for C\(_{20}\)H\(_{24}\)NaO\(_5\) ([M+Na]\(^+\)) calculated 367.1521, found 367.1516, \(\Delta\) +4.3 ppm.
**1,1,3,3-Tetrabromopropan-2-one**\(^{152}\)

![Tetrabromopropan-2-one](image)

\[
C_3H_2Br_4O \\
\text{Molecular weight: } 373.66 \text{ g.mol}^{-1}
\]

Bromine (65.0 mL, 1.27 mol) was added dropwise over 4 h to a stirred solution of acetone (25.0 mL, 0.340 mol) in hydrogen bromide (30.0 mL of a 48% aqueous solution, 0.270 mol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The solution was cooled to 0 °C then diluted with H\(_2\)O (200 mL) and CH\(_2\)Cl\(_2\) (300 mL). A saturated aqueous solution of NaHCO\(_3\) (300 mL) was added, then the two phases were separated and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (3 x 200 mL). The organic extracts were combined, washed with a saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (50 mL) and H\(_2\)O (150 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. The crude product was distilled under reduced pressure (130 °C, 15 mbar) to deliver a yellow oil. Crystallization using petroleum ether and EtOAc afforded tetrabromoacetone (52.2 g, 41% yield) as a colourless solid.

\[
R_f = 0.71 (\text{petroleum ether–Et}_2\text{O, 1:1}); \\
\text{IR: } \nu_{\text{max}} \text{ 3011, 1728, 1244, 1088, 1044 cm}^{-1}; \\
\text{m.p.} = 37–39 \degree \text{C}; \\
^1\text{H NMR: } (400 \text{ MHz, CDCl}_3) \delta_H 6.37 (2\text{H, s, CH-C2}); \\
^13\text{C NMR: } (101 \text{ MHz, CDCl}_3) \delta_C 183.6 (\text{C-C1}), 34.0 (2 \times \text{CH-C2}).
\]

**Preparation of Zn/Cu couple**\(^{164}\)

A suspension of activated zinc dust (20.2 g, 309 mmol) in degassed H\(_2\)O (80 mL) was treated with copper (II) sulfate (3.45 g, 21.6 mmol) and lead (II) chloride (433 mg, 1.50 mmol). The reaction mixture was stirred under an argon atmosphere for 45 min. The reaction mixture was filtered under argon and the black solid obtained washed with degassed H\(_2\)O (200 mL) and degassed acetone (200 mL). The Zn/Cu couple was dried at 100 °C under vacuum for 6 h, then stored under argon.
(1R*,5S*)-8-Oxabicyclo[3.2.1]oct-6-en-3-one (335)\(^1\)\(^2\)

\[
\begin{align*}
\text{C}_7\text{H}_8\text{O}_2 \\
\text{Molecular weight: 124.14 g.mol}^{-1}
\end{align*}
\]

Furan (11.1 mL, 153 mmol) was added to a suspension of activated zinc dust (7.40 g, 112 mmol) in anhydrous THF (25 mL). A solution of tetrabromoacetone (30.0 g, 102 mmol) and triethyl borate (22.5 mL, 132 mmol) in anhydrous THF (15 mL) was added dropwise over 15 min. After the addition of 80% of the tetrabromoacetone solution, bromine (0.3 mL) was added and then the addition was completed. The reaction mixture was warmed to 40 °C until the exothermic reaction started, then the oil bath was removed and the reaction stirred overnight at rt. The solution was cooled to −15 °C, the reaction was quenched with H\(_2\)O (30 ml) and the resulting mixture was stirred for 30 min at rt. The reaction mixture was filtered through a short pad of Celite and the pad washed with Et\(_2\)O (5 x 100 mL). The solution was washed with H\(_2\)O (2 x 150 mL) and brine (250 mL). The phases were separated and the aqueous phase extracted with Et\(_2\)O (2 x 150 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated under reduced pressure.

A solution of the residue material [64.4 mmol] in MeOH (30 mL) was added to a suspension of Zn/Cu couple (16.8 g) and NH\(_4\)Cl (10.3 g, 193 mmol) in MeOH (30 mL) at −78 °C. After 10% of the solution was added, the reaction mixture was stirred for 15 min at −78 °C then warmed to 0 °C. Addition of the solution was completed and the mixture was warmed to rt and stirred overnight. The resulting solution was filtered through a small pad of Celite and the pad washed with Et\(_2\)O (3 x 150mL). The combined filtrate was washed with brine (200 mL), then the phases were separated and the aqueous phase extracted with CHCl\(_3\) (4 x 100 mL). The organic extracts were combined, dried (MgSO\(_4\)) and concentrated under reduced pressure. Any remaining traces of HBr were removed by filtration through a small pad of K\(_2\)CO\(_3\) and the pad washed with CHCl\(_3\) (3 x 30 mL). Flash column chromatography (petroleum ether–Et\(_2\)O, 9:1 to 1:1) afforded 335 (3.59 g, 45% yield over two steps) as a pale yellow solid.
$R_f = 0.32$ (petroleum ether–Et$_2$O, 1:1);

m.p. = 39–41 °C;

IR: $\nu_{\text{max}}$ 2990, 2969, 2011, 1707, 1400, 1343, 1180, 1123, 1030 cm$^{-1}$;

$^1$H NMR: (500 MHz, CDCl$_3$) $\delta_H$ 6.26 (2H, s, CH–C4), 5.04 (2H, d, $J = 5.1$ Hz, CH-C3), 2.76 (2H, dd, $J = 17.0$, 5.1 Hz, CH$_2$-C2), 2.33 (2H, d, $J = 17.0$ Hz, CH$_2$-C2);

$^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta_C$ 205.4 (C–C1), 133.4 (CH–C4), 77.3 (CH-C3), 46.8 (CH$_2$-C2);

HRMS: (EI') for C$_7$H$_8$O$_2$ ([M]$^+$) calculated 124.0524, found 124.0522, $\Delta$ -1.5 ppm.

(1S*,2S*,5S*)-2-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (344)$^{152}$

\[
\text{C}_7\text{H}_8\text{O}_3
\]

Molecular weight: 140.14 g.mol$^{-1}$

$n$-Butyl lithium (13.0 mL, 2.5 M solution in hexanes, 32.6 mmol) was added to a freshly distilled solution of diisopropylamine (4.40 mL, 31.5 mmol) in anhydrous THF (20 mL) at -78 °C. The solution was warmed to rt, stirred for 30 min, then cooled to -78 °C. A solution of 335 (1.30 g, 10.5 mmol) in anhydrous THF (10 mL) was added, followed by the dropwise addition of TESCl (2.92 mL, 17.9 mmol) and Et$_3$N (3.80 mL, 27.3 mmol). The solution was stirred for 30 min at -78 °C and then the reaction was quenched with a saturated aqueous solution of NH$_4$Cl (110 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (125 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The resulting silyl enol ether 343 was used without further purification.

A freshly distilled solution of dimethyl dioxirane (130 mL of a 0.09 M solution in acetone, 11.6 mmol) was added to a solution of crude 343 [10.5 mmol] in anhydrous CH$_2$Cl$_2$ (120 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 3 h, concentrated under reduced pressure then diluted in THF:H$_2$O (2:1, 60 mL). The solution was cooled to 0 °C and AcOH (4 mL) was added. The reaction mixture was stirred for 1 h at 0 °C, then for 1 h at rt. The reaction was
quenched with saturated aqueous NaHCO₃ (75 mL) and solid NaHCO₃ (until gas evolution ceased). The phases were separated and the aqueous phase extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (250 mL), dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et₂O, 3:1) afforded the hydroxyketone 344 (529 mg, 36% yield over two steps) as a colourless solid.

R_f = 0.21 (petroleum ether–Et₂O, 1:1);
m.p. = 47–49 ºC;
IR: ν_max 3397, 2963, 1717, 1404, 1335, 1180, 1065, 1040, 1009 cm⁻¹;
¹H NMR: (400 MHz, CDCl₃) δ_H 6.40 (1H, ddd, J = 6.1, 1.7, 0.7 Hz, CH-C5), 6.21 (1H, dd, J = 6.1, 1.9 Hz, CH-C4), 5.05–5.00 (1H, m, CH-C6), 4.93 (1H, br s, CH-C3), 3.69 (1H, d, J = 7.2 Hz, CH-C2), 3.20 (1H, d, J = 7.2 Hz, OH), 3.05 (1H, dd, J = 16.6, 5.1 Hz, CH₂-C7), 2.32 (1H, d, J = 16.6 Hz, CH₂-C7);
¹³C NMR: (101 MHz, CDCl₃) δ_C 204.9 (C-C3), 136.7 (CH-C6), 129.6 (CH-C7), 82.5 (CH-C1), 77.5 (CH-C5), 75.5 (CH-C2), 44.6 (CH₂-C4);
HRMS: (EI') for C₇H₈O₃ ([M]+) calculated 140.0473, found 140.0470, Δ -2.2 ppm.

Preparation of 4-methoxybenzyltrichloroacetamidate

A solution of 4-methoxybenzyl alcohol (5.80 mL, 46.7 mmol) was added to a suspension of sodium hydride (200 mg of a 60% dispersion in mineral oil, 8.33 mmol) in anhydrous Et₂O (40 mL). The reaction mixture was cooled to 0 ºC and stirred for 15 min. Trichloroacetonitrile (5.00 mL, 50.0 mmol) was added dropwise and the solution stirred for 30 min at 0 ºC, then for 45 min at rt. The solution was diluted with Et₂O (150 mL) and the reaction was quenched with a saturated aqueous solution of NaHCO₃ (150 mL). The phases were separated and the organic phase washed with brine (150 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude acetamidate (11.7 g) was used without further purification.
Camphorsulfonic acid (671 mg, 2.89 mmol) and a solution of 344 (4.02 g, 28.9 mmol) in anhydrous CH₂Cl₂ (35 mL) were added to a solution of 4-methoxybenzyltrichloroacetamidate (7.24 g, 31.2 mmol) in anhydrous CH₂Cl₂ (30 mL) at 0 ºC. The reaction mixture was warmed to rt and stirred overnight. The solution was diluted with Et₂O (300 mL) and the organic phase washed with a saturated aqueous solution of NaHCO₃ (100 mL) and brine (100 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et₂O, 9:1 to 3:2) afforded 345 (6.32 g, 84% yield) as a colourless solid.

R_f = 0.43 (petroleum ether—Et₂O, 1:1);
m.p. = 61—63 ºC;
IR: ν_{max} 2957, 2841, 1707, 1613, 1512, 1470, 1331, 1238, 1173, 1086, 1059 cm⁻¹;
¹H NMR: (500 MHz, CDCl₃) δ_H 7.29 (2H, d, J = 8.6 Hz, CH-11), 6.88 (2H, d, J = 8.6 Hz, CH-10), 6.39 (1H, dd, J = 6.0, 1.2 Hz, CH-C5), 6.11 (1H, dd, J = 6.0, 1.8 Hz, CH-C4), 5.02 (1H, ddd, J = 4.8, 1.2, 1.2 Hz, CH-C6), 4.91 (1H, br s, CH-C3), 4.67 (1H, d, J = 11.9 Hz, CH₂-C8), 4.44 (1H, d, J = 11.9 Hz, CH₂-C8), 3.80 (3H, s, CH₃-C13), 3.39 (1H, s, CH₂-C2), 3.07 (1H, dd, J = 16.1, 4.8 Hz, CH₂-C7), 2.32 (1H, d, J = 16.1 Hz, CH₂-C7);
¹³C NMR: (126 MHz, CDCl₃) δ_C 203.7 (C-C1), 159.6 (C-C12), 137.3 (CH-C5), 130.1 (2 x CH-11), 129.5 (CH-C4), 129.4 (C-C9), 114.0 (2 x CH-10), 81.4 (CH-C3), 79.9 (CH-C2), 77.5 (CH-C6), 71.9 (CH₂-C8), 55.4 (CH₃-C13), 45.5 (CH₂-C7);
HRMS: (EI⁺) for C₁₅H₁₆O₄ ([M⁺]⁺) calculated 260.1049, found 260.1046, Δ = −0.9 ppm.
(1S*,2S*,4R*,5R*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (347)\textsuperscript{125}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) [draw, circle] {O};
\node (b) at (0.5,0) [draw, circle] {O};
\node (c) at (1,0) [draw, circle] {O};
\node (d) at (1.5,0) [draw, circle] {O};
\node (e) at (2,0) [draw, circle] {O};
\node (f) at (2.5,0) [draw, circle] {O};
\node (g) at (3,0) [draw, circle] {O};
\node (h) at (3.5,0) [draw, circle] {O};
\node (i) at (4,0) [draw, circle] {O};
\node (j) at (4.5,0) [draw, circle] {O};
\node (k) at (5,0) [draw, circle] {O};
\node (l) at (5.5,0) [draw, circle] {O};
\node (m) at (6,0) [draw, circle] {O};
\node (n) at (6.5,0) [draw, circle] {O};
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\node (p) at (7.5,0) [draw, circle] {O};
\node (q) at (8,0) [draw, circle] {O};
\node (r) at (8.5,0) [draw, circle] {O};
\node (s) at (9,0) [draw, circle] {O};
\node (t) at (9.5,0) [draw, circle] {O};
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\node (v) at (10.5,0) [draw, circle] {O};
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\node (x) at (11.5,0) [draw, circle] {O};
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\node (z) at (12.5,0) [draw, circle] {O};
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\node (B) at (0.5,0) [draw, circle] {2};
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\node (H) at (3.5,0) [draw, circle] {8};
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\end{tikzpicture}
\end{center}

\text{C}_{15}\text{H}_{16}\text{O}_5

\text{Molecular weight: 276.28 g.mol}^{-1}

\text{n-Butyl lithium (0.80 mL 2.5 m solution in hexanes, 2.0 mmol) was added to a freshly distilled solution of diisopropylamine (0.27 mL, 1.9 mmol) in anhydrous THF (5 mL) at \text{-78 °C}. The solution was warmed to rt, stirred for 30 min then cooled to \text{-78 °C}. A solution of 345 (251 mg, 0.960 mmol) in anhydrous THF (3 mL) was added, followed by the dropwise addition of TESCl (0.27 mL, 1.6 mmol) and Et}_3\text{N (0.35 mL, 2.5 mmol). The solution was stirred for 30 min at \text{-78 °C} and then the reaction was quenched with a saturated aqueous solution of NH}_4\text{Cl (10 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 25 mL). The organic extracts were combined, washed with brine (20 mL), dried (MgSO}_4 and concentrated under reduced pressure. The resulting silyl enol ether 346 was used without further purification.}

\text{A freshly distilled solution of dimethyl dioxirane (11.8 mL of a 0.09 m solution in acetone, 1.06 mmol) was added to a solution of crude 346 [0.960 mmol] in anhydrous CH}_2\text{Cl}_2 (15 mL) at \text{-78 °C}. The reaction mixture was stirred at \text{-78 °C} for 3 h, concentrated under reduced pressure and then diluted in THF:H}_2\text{O (2:1, 9 mL). The solution was cooled to 0 °C and AcOH (0.4 mL) was added. The reaction mixture was stirred for 1 h at 0 °C, then warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NaHCO}_3 (10 mL) and solid NaHCO}_3 (until gas evolution ceased). The phases were separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (30 mL), dried (MgSO}_4 and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et}_2\text{O, 9:1 to 1:1) afforded hydroxyketone 347 (154 mg, 58% over two steps) as a colourless solid.}
\( R_f = 0.21 \) (petroleum ether–Et\(_2\)O, 1:1);
m.p. = 105–107 °C;
IR: \( \nu_{\text{max}} \) 3403, 1722, 1614, 1514, 1398, 1250, 1177, 1074, 1044, 1032, 1005 cm\(^{-1}\);

**\(^1\)H NMR:** (500 MHz, CDCl\(_3\)) \( \delta_H \)

- 7.29 (2H, d, \( J = 8.6 \) Hz, CH–11), 6.89 (2H, d, \( J = 8.6 \) Hz, CH–C10), 6.32 (1H, dd, \( J = 6.1, 1.7 \) Hz, CH–C5), 6.23 (1H, dd, \( J = 6.1, 1.7 \) Hz, CH–C4), 4.95–4.92 (2H, m, CH–C3 and CH–C6), 4.68 (1H, d, \( J = 11.4 \) Hz, CH–C7), 3.56 (1H, dd, \( J = 1.4, 1.3 \) Hz, CH–C2), 3.45 (1H, d, \( J = 10.8 \) Hz, OH);

**\(^13\)C NMR:** (126 MHz, CDCl\(_3\)) \( \delta_C \)

- 202.1 (C–C1), 159.8 (C–C12), 132.9 (CH–C5), 132.4 (CH–C4), 130.3 (CH–C11), 128.9 (C–C9), 114.1 (CH–10), 83.1 (CH–C6), 81.8 (CH–C2), 81.6 (CH–C3), 77.3 (CH–C7), 72.2 (CH–C8), 55.4 (CH–C13);

**HRMS:** (El.) for C\(_{15}\)H\(_{16}\)O\(_5\) ([M]+) calculated 276.0998, found 276.0997, Δ –0.2 ppm.

\((1R^*, 2R^*, 4S^*, 5S^*)-2, 4\text{-Bis[}(4\text{-methoxybenzyl})\text{oxy}]\text{-8-oxabicyclo[3.2.1]oct-6-en-3-one (348)\(^{125}\)}\)

Camphorsulfonic acid (19.0 mg, 0.0800 mmol) and a solution of 347 (220 mg, 0.810 mmol) in anhydrous CH\(_2\)Cl\(_2\) (5 mL) were added to a solution of 4-methoxybenzyltrichloroacetamidate (230 mg, 0.920 mmol) in anhydrous CH\(_2\)Cl\(_2\) (5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The solution was diluted with Et\(_2\)O (20 mL) and washed with a saturated aqueous solution of NaHCO\(_3\) (20 mL) and brine (20 mL). The organic phase was dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether–Et\(_2\)O, 9:1 to 1:1) afforded 348 (202 mg, 63% yield) as a colourless solid.

\( R_f = 0.37 \) (petroleum ether–Et\(_2\)O, 1:1);
m.p. = 87–89 °C;
IR: \( \nu_{\text{max}} \) 2955, 2891, 1713, 1613, 1512, 1458, 1302, 1238, 1175, 1065, 1034 cm\(^{-1}\);
\textbf{^1\text{H NMR}}: (500 MHz, CDCl$_3$) \(\delta_H 7.31\) (4H, d, \(J = 8.6\) Hz, CH-C8), 6.87 (4H, d, \(J = 8.6\) Hz, CH-C7), 6.21 (2H, s, CH-C4), 4.93 (2H, s, CH-C3), 4.74 (2H, d, \(J = 11.9\) Hz, CH$_2$-C5), 4.49 (2H, d, \(J = 11.9\) Hz, CH$_2$-C5), 3.80 (6H, s, CH$_3$-C10), 3.43 (2H, s, CH-C2);

\textbf{^13\text{C NMR}}: (126 MHz, CDCl$_3$) \(\delta_C 202.6\) (C-C1), 159.6 (2 x C-C9), 133.0 (2 x CH-C4), 130.1 (4 x CH-C8), 129.5 (2 x C-C6), 114.0 (4 x CH-C7), 81.4 (2 x CH-C3), 79.9 (2 x CH-C2), 71.8 (2 x CH$_2$-C5), 55.4 (2 x CH$_3$-C10);

\textbf{HRMS}: (ESI) for C$_{23}$H$_{24}$NaO$_6$ ([M+Na]$^+$) calculated 419.1471, found 419.1465, \(\Delta +0.2\) ppm.
Chapter 4: References
Chapter 4: References


Grainge, D. M., Unpublished work.


136 Sparenberg, M., Unpublished work.


Appendix A: NOE correlations
<table>
<thead>
<tr>
<th>Compound</th>
<th>% NOE enhancements</th>
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</tr>
<tr>
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<td><img src="image" alt="Chemical Structure" /> 1% 1.5%</td>
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Appendix B: Selected $^1\text{H}$ and $^{13}\text{C}$ spectra